Entheogens, the Conscious Brain and Existential Reality

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Complementary video: Entheogens, Culture and the Conscious Brain http://youtu.be/pY2MDqdv-No

Abstract: *The purpose of this article is to provide a 'state of the art' research overview of what is currently known about how entheogens, including the classic psychedelics, affect the brain and transform conscious experience through their altered receptor dynamics, and to explore their implications for understanding the conscious brain and its relationship to existential reality, and their potential utility in our cultural maturation and understanding of the place of sentient life in the universe.*

Contents

1: Cultural and Historical Introduction

Human societies have been actively using psychoactive substances since the earliest cultures emerged. In "The Alchemy of Culture" Richard Rudgley notes that European cave depictions, from the paleolithic on, abound with both herbivorous animals of the hunt and geometrical entopic patterns similar to the phosphenes seen under sensory withdrawal and under the effects of psychotropic herbs. By the time we find highly-decorated pottery 'vase supports' in Middle Neolithic France, we have evidence consistent with their ritual use as opium braziers. At 4200 BC at the Cueva de los Murciélagos site in Spain we find burials with bags containing *Papaver somniferum* capsules. During the 18th Egyptian dynasty 1550-1295 BC there was an active trade with Cyprus of juglets, whose form is neatly in the shape of an inverted poppy pod, indicating they contained opium. This trend is confirmed in detail in the terracotta Goddess figurines discovered from a small shrine at Gazi west of Knossos in Crete, dated to 1350 BC, whose headdress consists of a row of three poppy heads explicitly slit in the exact way opium resin is extracted from the poppy to this day. A goddess with the same emblems - three poppies - in her hand is depicted also in a gold signet ring from Mycenae from 1500 BC.

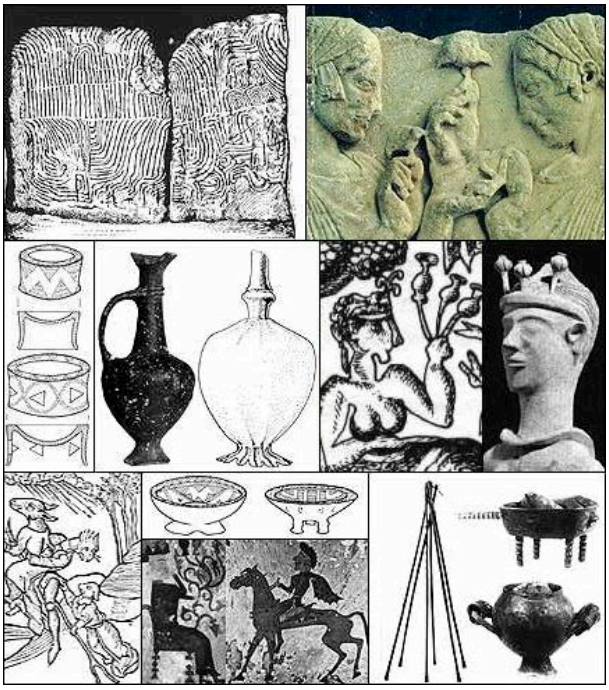


Fig 1: Phosphene-like finger markings Neolithic tomb of Gaverinus, Brittany. Persephone passing what looks like a liberty bell psilocybe to Demeter, Er Lannic pottery possibly used for opium, opium juglets from Cyprus (Rudgley), poppies being offered and the poppy goddess with slit poppy heads on her crown, the oldest illustration of witches, polyploidy bowls which may have been used for vaporizing cannabis, the Scythian goddess showing a horseman the tree of life, braziers and pots in the Scythian ritual use of cannabis (Schultes & Hofmann).

The earliest cultural evidence of Cannabis comes from the oldest known Neolithic culture in China, the Yang-shao, which appeared along the Yellow River valley about 6,500 years ago. The clothes the people wore, the nets they fished and hunted with, and the ropes they used in their earliest machines was said to made from hemp. Evidence for *Cannabis sativa*

use in Europe also dates back to the neolithic, where there is evidence that it was used for rope and for its psychotropic and potentially hallucinogenic effects. Polyploid bowls with rope imprints again look to be braziers for consuming plant vapours. Pipe cups dating from a third millennium BC burial site in Romania explicitly contain charred hemp seeds, consistent with their being the remains of a smoked cannabis pipe. According to The Living Torah kaneh-bosm (Hebrew: בֹּשֶׂם-קָנֶה) identified with cannabis may have been one of the ingredients of the holy anointing oil mentioned in various sacred Hebrew texts. The Scythians of southern Central Asia used Cannabis to attain trance during funeral rites, using a metal tripod censer. Censers have been found still containing hemp seed (Rudenko). Herodotus, more than 2000 years ago, described the way Scythians burned portions of the plant in metal tripod censers, beneath small tent structures that enclosed the vapors inhaled for ritualistic and euphoric purposes (Merlin, Schultes & Hofmann). "The Scythians then take this seed of hemp and, creeping under the mats, they throw it on the red-hot stones; and, being so thrown, it smolders and sends forth so much steam that no Greek vapour bath could surpass it. The Scythians howl in their joy at the vapour bath." The Yanghai Tombs of Xinjiang have revealed the 2700-year-old grave of a shaman. Near the head and foot was a large leather basket and wooden bowl filled with 789g of cannabis, superbly preserved by climatic and burial conditions. This material still contained the active ingredient THC. Cannabis use in the Indian subcontinent may also go back to the earliest cultures. Cannabis is first referred to in Hindu Vedas between 2000 and 1400 BC, in the Atharvaveda. Shiva, who is the patron deity of Cannabis, can be seen in Mohenjo-Daro in a meditating pose with trident, as Pashupatinath Lord of the Animals surrounded by his beasts. Cannabis or Ganga carries the name of the sacred river itself, and the endocannabinoid anandamide was named after bliss.

Likewise by the fourth millennium BC, we also find evidence of alcohol use, probably initially from date palms and then the grape vine *Vitis vinifera*. Barley beer is referred to in early Sumerian and Akkadian texts. The soma or haoma of the Indo-Aryans extolled in the Rig Veda and the Avesta remains a botanical enigma, but nevertheless shows another psychotropic concoction which was extolled to semi-divine status, which has been attributed to Syrian rue *Peganum harmala* which contains psychoactive monoamine oxidase inhibitor harmaline and to the muscimol-containing *Amanita muscaria* which has also been ritually used by Siberian shamans, because references to it suggest it was recycled in excreted urine. There is also an enigma surrounding the Eleusian epoptea which was said to be a sacramental repast of visionary transformative power, which has been associated with various psychotropic agents, including the liberty cap Psilocybe species which Persephone appears to be passing to Demeter on a stele as noted by Graves (O'Prey), and ergot fungus containing rye (Wasson et al).

In medieval times, in the midst of Christian persecution against all manner of heretics, witches and mystics, stemming from the Crusade against the Albigenses, there are also frequent references to the use of 'devilish' witching herbs which were an underlying part of pre-Christian European history and folklore, including Mandrake, Henbane, and Belladonna which are highly toxic deliriants which were rubbed on the body as herbal ointments causing sensations of flying, joining the sabbat, or lovemaking with an imagined suitor, due to the libido enhancing effects of hyoscyamine, and related muscarinic acetyl-choline receptor antagonists, followed by unconsciousness. These were pursued by the Inquisitors, as evidence of witchcraft and their practitioners condemned to death by drowning or burning at the stake. To compound matters, there were also episodes of mass poisoning due to lysergic acid derivatives in ergot fungus on the rye, resulting in outbreaks of collective madness, sometimes accompanied by the loss of appendages from gangrene caused by the vasoconstrictive effects of the alkaloids.

The term entheogen is derived from ancient Greek, ἔνθεος (entheos) "full of the god, inspired, possessed," the root of the English word 'enthusiasm', and γενέσθαι (genesthai) "to come into being." Thus, an entheogen is a substance that causes one to become inspired or to experience feelings of inspiration, often in a religious or "spiritual" manner. In a strict sense, only those vision-producing drugs that can be shown to have figured in shamanic or religious rites would be designated entheogens, but in a looser sense, the term can also be applied to other drugs, both natural and artificial, that induce alterations of consciousness similar to those documented for ritual ingestion of traditional entheogens. Evidence for the first use of entheogens may come from Tassili, Algeria, with a cave painting of a mushroom-man, dating to 8000 BP and mushroom idols from the Konya plain and the Vinca site in Europe (McKenna).

Part of the difficulty facing the acceptance of entheogens in European culture is that the most potent psychedelic entheogens have natural habitats in the Americas, where European cultures have come upon them as alien diabolical practices by often violent warrior pre-Colombian cultures such as the Aztecs, who themselves had horrific sacrificial practices worshipping gods of war regarded as heathen and devilish by the conquistadores. Christianity and conservative European culture, still reeling from its own paranoid

religious conflicts, as flagellating Penitente Catholics set out for a new world, regarded all such practices with horror, and although Christianity was also a sacramental religion with an equally bloodthirsty Eucharist of the *soma* and *sangre* of Christ, violently repressed all such use of visionary sacraments.

Nevertheless potent psychedelic entheogens were ritually used and held sacred by diverse pre-Colombian cultures for centuries and even millennia before the arrival of Columbus. Long before the Aztecs the Mayans record the use of sacred mushrooms belonging to the *Psilocybe* genus in both frescos and mushroom stones dating back as far as 1000 BC which show obvious evidence of use as a visionary agent. The sacred use of the mushroom *teonanactl* or 'flesh of the gods' continued as an unbroken tradition for 1,500 years to Columbus and then secretly for another 500 years to the present day.

The Aztecs a particularly vicious sacrifical warrior culture nevertheless freely embraced sacred mushrooms in their own frenzied way, seen through the distorting prisms of Conquistador diabolization. Friar Sahagun, one of the first conquistadors to chronicle *teonanacatl*, flesh of the gods, remarked:

"when they become excited by them start dancing, singing, weeping. Some do not want to sing but sit down and see themselves dying in a vision; others see themselves being eaten by a wild beast; others imagine they are capturing prisoners of war, that they are rich, that they possess many slaves, that they have committed adultery and were to have their heads crushed for the offence . . . and when the drunken state had passed, they talk over amongst themselves the visions they have seen" (Schultes and Hofmann 1979 146).

"During the coronation feast of Moctezuma in 1502, teonanacatl (the divine mushroom) was used to celebrate the event. War captives were slaughtered in great numbers to honour Moctezuma's accession to the throne. Their flesh was eaten, and a banquet was prepared after the victims' hearts were offered to the gods. After the sacrifice was over, everyone was bathed in human blood. Raw mushrooms were given to the guests, which one writer described as causing them to go out of their minds-in a worse state than if they had drunk a great quantity of wine. In his description, these men were so inebriated that many took their own lives. They had visions and revelations about the future, and Duran thought the devil was speaking to them in their madness. When the mushroom ceremony ended, the invited guests left. Moctezuma invited rival rulers to feasts which were held three times a year. One of these important feasts was called the Feast of Revelations, when the invited dignitaries and Moctezuma, or his representative, ate the wild mushrooms. " ... "During the Aztec king Tizoc's enthronement feast, all those present ate wild mushrooms - the kind that made men lose their senses. After four days of feasting, the newly crowned Tizoc gave his guests rich gifts and sacrificed the Metztitlan victims" (Dobkin de Rois 142).

By contrast the Mazatecs continued to use sacred mushrooms for divination and curing maladies in absolute secret, a secret so assiduously kept that all trace of magic mushroom worship became lost to the world at large until Maria Sabina accepted Gordon Wasson into the mysteries of the little flowers.

At the same time, Mexico was rich with other entheogenic sacraments. Various peoples consumed the mescalin-containing cactus *peyotl* or 'hairy one', the Huichols undertaking an annual pilgrimage across Mexico to collect it from the high deserts around their sacred mountain of Wirikuta, describing the effects of the cactus as opening the *nierika* or portal to the spirit world where everything becomes one:

"There is a doorway within our minds that usually remains hidden and secret until the time of death. The Huichol word for it is nieríka. Nieríka is a cosmic portway or interface between so-called ordinary and non-ordinary realities. It s a passageway and at the same time a barrier between the worlds. … When the mara'akáme passes through the nieríka [visionary tunnel] he moves just as the smoke moves; hidden currents carry him up and in all directons at once ... as if upon waves, flowing into and through other waves ... the urucate. As the mara'akáme descends and passes through the nieríka on the return, his memory of the urucate and their world fades; only a glimmer remains of the fantastic journey that he has made" (Halifax 239).

Evidence of peyote use goes back to the Toltecs in 500 BC where a snuffing pipe with a deer holding a peyote in its mouth has been found at Monte Alban. Others used the lysergic acid amide containing black seeds or *bardo negroh* of the morning glory, and the Herb of the Shepherdess, *Salvia divinorum* to induce visions when sacred mushrooms were not available.

In the southern continent, an equally diverse spectrum of entheogenic sacraments had been discovered, from the mescalin-containing San Pedro cactus *Trichocereus pachanoi* (holding the keys to the golden gate), through snuffs such as and *epena* from *Virola* species and the famous pan-Amazonian brew *ayahuasca* of "Vine of the Soul" containing DMT from plants such as *Psychotria viridis*, beta-carboline MAO inhibitors such as harmine from the vine *Banisteriopsis caapi* and occasionally solonaceous alkaloids from *Brugmansia* a tree-datura having deliriant effects similar to the witching herbs of Old Europe.

Archaeological records of sacred use likewise go back to ancient times, with evidence of San Pedro use, in the cactus found alongside a leopard in Chavin culture (1200-600 BC), evidence of sacred mushroom use in Paracas culture (800-100 BC), and San Pedro and snuff use among Nazca (100-800 CE). As well, as an energetic mainstay and spiritual guide, the coca leaf was chewed, along with stimulants such as caffeine.

Likewise in the African subcontinent, two of the oldest human cultures the Bushmen and Pygmies have traditional sacred use of psychotropics. Biaka pygmies use the hallucinogen *Tabernanthe iboga* and there is also a pattern of Cannabis use among the Bushmen, to complement their trance dancing visitations. Although this is an imported tradition, it is done in a unique ancient manner, filling a hole in the ground with plant material, from which the herb is smoked cool.

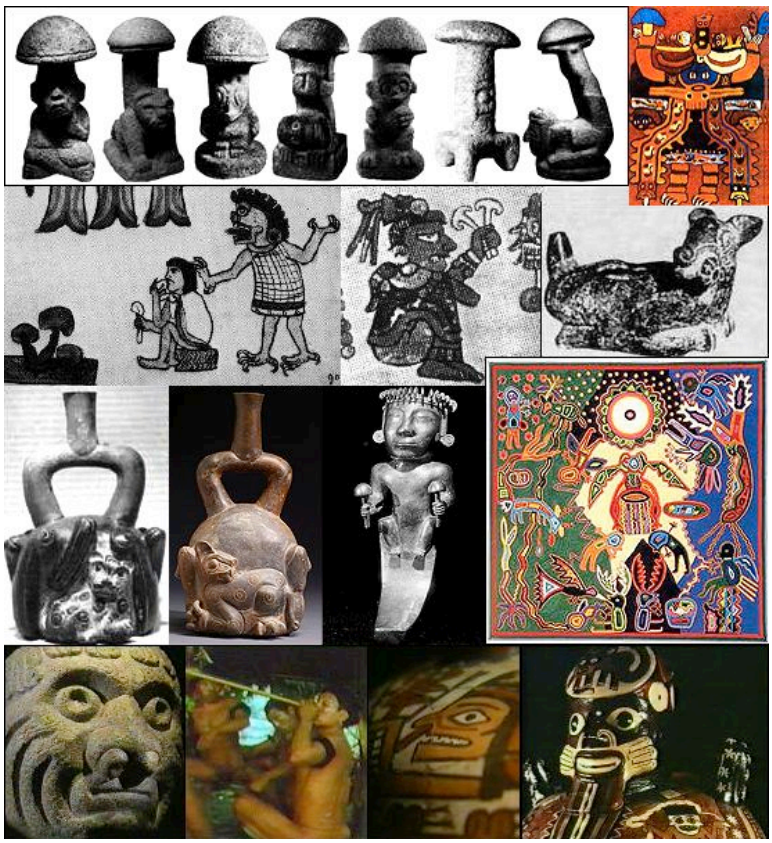


Fig 2: Diverse sacramental use over millennia in the Americas. Mayan sacred mushroom stones, a blue topped mushroom carried by a shaman Paracas culture, Aztec murals showing sacred mushroom deities (Magliabecciano Codex), the deer snuffing pipe holding a peyote from Monte Alban, two Chavin urns with jaguar beside San Pedro cacti, a sacred mushroom deity from South America the Huichol nierika or visionary portal opened by peyote, a Chavin statue and Nazca gourd showing hallucinogenic snuffing , and a Nazca pottery showing San Pedro use.

We need to examine at this point why diverse pre-Columbian cultures have consistently managed to incorporate enthogens successfully into their highest cultural expressions, remaining as a spiritual record for archaeologists to discover, while so-called emancipated Western society has made them an absolute taboo, ring-fenced by dire penalties of long-term imprisonment or even death, amid threats of insanity and permanent brain, or genetic damage.

We can again see currents of the schizophrenic attitude of Western society to psychotropic agents in its romantic and demonic attitudes to opium and cocaine. While Samuel Taylor Coleridge composed “Kubla Khan” in 1797, according to his preface, one night after he experienced an opium influenced dream, and Sigmund Freud extolled the virtues of cocaine in his 1884 paper "On Coca", Great Britain had become deeply involved in the trafficking of opium from factories in India to China, against Chinese legislation, in the Opium Wars (1839-1860) with the explicit purpose of addicting the Chinese population, to redress an unfavourable trade balance between the countries. At the same time the Victorian press was hot with scandalous stories of debauchery and dissolution in the opium dens of London. By 1886 Arthur Conan Doyle was writing of the hideous dependence of Sherlock Holmes on cocaine injection and the stage was again set for regarding psychotropic drugs as agents of evil.

At the turn of the twentieth century, long after its spread to the plains Indians in the 15th century, there had been a resurgence of religious peyote use in the US in the form of the Native American Church (Anderson), which has fought a long and tortuous battle for the legal use of the sacrament.

Speak to the peyote with your heart, with your thoughts. And the peyote sees your heart ...
And if you have luck, you will hear thingsand receive things that are invisible to others,
but that god has given you to pursue your path(Schultes and Hofmann).

"God told the Delawares to do good even before
He sent Christ to the whites who killed him ...
God made Peyote It is His power. It is the power of Jesus.
Jesus came afterwards on this earth, after peyote." (Anderson).

In 1897 Arthur Heffter isolated the alkaloid mescalin from peyote and the modern era of psychedelic, or “mind manifesting” research began. William James author of “Varieties of Religious Experience” who had tried many psychoactive agents unfortunately had a bad intestinal reaction in 1896 and missed out on its “chromatic” effects, but noted "all kind of odd experiences, mescal, ecstasies etc. give them indeterminate possibilities". It is said that round 1911 the young Adolf Hitler took peyote during his formative period, provided him by apothecary Wilhelm Pretzsche (Andrews 417-425). In 1938 Albert Hofmann synthesized LSD, but had to wait five years before accidentally absorbing enough on his fingers in 1943 to discover its psychedelic effects. Interviewed shortly before his hundredth birthday, he called LSD "medicine for the soul" and was frustrated by the subsequent worldwide prohibition of it. Nevertheless for several decades these substances remained research materials and were not regarded as dangerous drugs of abuse.

While both opium and cocaine had essentially been legal in the 1800s, cultural migration had begun to cause social problems both through patterns of addiction and through racial prejudice and cultural profiling. Chinese populations in the US were perceived to be addicted to opium and Negro populations were accused of abusing cocaine resulting in rape of white women and improved marksmanship among criminals. A series of tax and drug laws were passed leading to successively tighter restrictions. By 1930 the newly formed Federal Bureau of Narcotics, headed by Harry J. Anslinger, as part of the government's broader push, to outlaw all recreational drugs, advertising marijuana as a “killer drug” inviting “Murder! Insanity!” and “Death!” By 1935 the Geneva Trafficking Conventions outlawed international trafficking in opium, cocaine and cannabis, but the US, headed by Anslinger, refused to sign the final draft because it didn’t include cultivation, production, manufacture and distribution and considered it too weak in relation to extradition, extraterritoriality and the confiscation of trafficking profits. Given these Calvinistic attitudes, it is not hard to understand how the vastly more confounding entheogens might come to be treated.

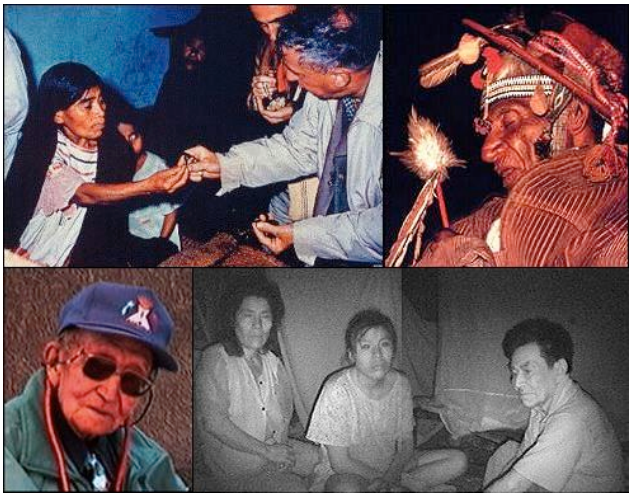


Fig 3: Maria Sabina passing the sacred mushroom to Gordon Wasson (Riedlinger). The renowned Huichol elder Don Jose Matsuwa (Schultes & Hofmann), Tellus ‘Goodmorning’, the roadman at my first peyote meeting in 1976, attending his son’s meeting in 1992 at the age of 93. Senor Trinico by infra-red video in the dark during our ayahuasca ceremony in 1999.

All records of sacred mushroom use had been lost to history by the turn of the 20th century and it had become assumed that the sacred mushroom was a case of mistaken identity for peyote. However in 1938 Blas Reko and Richard Evans Schultes traveled to Huautla de Jiménez, where Robert Weitlaner had a year earlier located a specimen and managed to find four species of *Paneolus* and *Psilocybe*, including *caerulescens* and *cubensis* (Ott). A year later Weitlaner’s daughter Irmgard witnessed a mushroom velada without partaking, but war intervened. Then in 1953 Gordon Wasson would finally meet Maria Sabina the Mazatec curandero, in Huautla, after strong encouragement from Robert Graves.

It was in his own words, an entheogen - "the divine mushroom of immortality", calling it "Ecstasy!" after Greek *ekstasis* - flight of the soul from the body. “In truth he is the five senses disembodied, all of them keyed to the height of sensitivity, and awareness, all of them blending into one another most strangely until, utterly passive he becomes a pure receptor infinitely delicate of sensation. … Your very soul is seized and shaken until it tingles, until you feel that you will never recover your equilibrium”. He also noted that Greeks call mushrooms *broma theon* "the food of the gods" and specifically likened the experience to the epoptea of Eleusis "For me there is no doubt that the secret of Eleusis lies in hallucinogens". Wasson was to describe the experience as Pentecost and the long-held secret of sacred mushroom again greeted the world. "By comparison with the mushroom, the Element in the Christian agape seems pallid. The mushroom holds the key to a mystical union with God, whereas only rare souls can attain similar ecstasy and divine communion by intensive contemplation of the miracle of the Mass" (Riedlinger, Furst).

"On both nights RGW stood up for a long time in Cayetano's room at the foot of the stairway, holding on to the rail transfixed in ecstasy by the visions that he was seeing in the darkness with his open eyes. For the first time that word 'ecstasy' took on a subjective meaning for him. ... There came one moment when it seemed as though the visions themselves were about to be transcended, and dark gates reaching upward beyond sight were about to part, and we

were to find ourselves in the presence of the Ultimate. We seemed to be flying at the dark gates as a swallow at a dazzling lighthouse, and the gates were to part and admit us. But they did not open, and with a thud we fell back gasping. We felt disappointed, but also frightened and half relieved, that we had not entered into the presence of the ineffable, whence, it seemed to us at the time, we might not have returned, for we had sensed that a willing extinction in the divine radiance had been awaiting us. … The spirit of the agape of which we have already spoken was a prelude to a wave of generous tender feelings that the mushroom aroused in everyone ... Twice in the course of the night the Senora reached out her right hand to me and sought contact with my fingers in friendly greeting, across the chasm of the language barrier - Gordon Wasson & Valentina Wasson - Mushrooms Russia & History (Riedlinger).

To Maria Sabina, although also using it for curing maladies, it was also an entheogen, reciting it's illumination in her chants:

"Woman who thunders am I, woman who sounds am I.
Spiderwoman am I, says hummingbird woman am I says
Eagle woman am I, says important eagle woman am I.
Whirling woman of the whirlwind am I, says
woman of a sacred, enchanted place am I, says
Woman of the shooting stars am I. ...
I'm a birth woman, says I'm a victorious woman, says
I'm a law woman, says I'm a thought woman, says I'm a life woman,
I am a spirit woman, says I am a crying woman, says
I am Jesus Christ, says ... I'm the heart of the virgin Mary."
(Mushroom Ceremony - Smithsonian Institute)

Her vision of the inner world of the sacred mushroom is both entheogenic and prophetic:

"There is a world beyond ours, a world that is far away, nearby and invisible. And there is where God lives, where the dead live, the spirits and the saints, a world where everything has already happened and everything is known. That world talks. It has a language of its own. I report what it says. The sacred mushroom takes me by the hand and brings me to the world where everything is known. It is they, the sacred mushrooms that speak in a way I can understand. I ask them and they answer me. When I return from the trip that I have taken with them I tell what they have told me and what they have shown me. The more you go inside the world of teonanacatl , the more things are seen. And you also see our past and our future, which are there together as a single thing already achieved, already happened . . . I saw stolen horses and buried cities, the existence of which was unknown, and they are going to be brought to light. Millions of things I saw and knew. I knew and saw God: an immense clock that ticks, the spheres that go slowly around, and inside the stars, the earth, the entire universe, the day and the night, the cry and the smile, the happiness and the pain. He who knows to the end the secret of teonanacatl - can even see that infinite clockwork" (Schultes & Hofmann).

The reaction of the US government was swift. Within a few days, a Mexican botanist had phoned the CIA to confirm Wassons find, and a CIA agent James Moore was dispatched as a mole on Wasson's return trip, so that the government could use it as a mind-altering drug in chemical warfare and interrogation, in Project MKULTRA, demonstrating the Western establishment's proactively malign attitude and complete failure to understand the nature and potential social benefits of entheogenic sacraments (Riedlinger), also implicated in the mass hallucinogenic poisoning at Pont-Saint-Esprit Frace in 1951 (Thomson).

In 1948, Rappoport had discovered a hormone, named serotonin for its effect on vascular tone in cow blood serum, which was identified in 1952 to be 5-hydroxytryptamine, or 5HT, and was discovered in high concentrations in brain tissue in 1953. By 1954 Gaddum and Hameed, and Woolley and Shaw, both suggested the effects of LSD might arise from 5HT receptor agonism, or antagonism, because of the obvious similarity with psilocin (Braden). However as late as 1973 electron donation was still being advanced for the 'LSD receptor' for the obvious reason that serotonin itself, although a 5HT receptor agonist, did not cause hallucinations (Nature 242, 367).

By 1954 Aldous Huxley had captured the imagination of young readers in his description in "The Doors of Perception" of his experiences with mescalin:

"Confronted by a chair which looked like the Last Judgment - or, to be more accurate, by a Last Judgment which, after a long time and with considerable difficulty, I recognized as a chair - I found myself all at once on the brink of panic. This, I suddenly felt, was going too far. Too far, even though the going was into intenser beauty, deeper significance. The fear, as I analyze it in retrospect, was of being overwhelmed, of disintegrating under a pressure of reality greater than a mind, accustomed to living most of the time in a cosy world of symbols, could possibly bear. The literature of religious experience abounds in references to the pains and terrors overwhelming those who have come, too suddenly, face to face with some manifestation of the Mysterium tremendum. In theological language, this fear is due to the incompatibility between man's egotism and the divine purity, between man's self-aggravated separateness and

the infinity of God. Following Boehme and William Law, we may say that, by unregenerate souls, the divine Light at its full blaze can be apprehended only as a burning, purgatorial fire. An almost identical doctrine is to be found in The Tibetan Book of the Dead, where the departed soul is described as shrinking in agony from the Pure Light of the Void, and even from the lesser, tempered Lights, in order to rush headlong into the comforting darkness of selfhood as a reborn human being, or even as a beast, an unhappy ghost, a denizen of hell. Anything rather than the burning brightness of unmitigated Reality - anything!"

The eloquently expressed popularity of these agents began to illuminate the public imagination, particularly among young people breaking out of a conservative post-war colonial Christian straight-jacket. From 1960 to 1962, Timothy Leary, Richard Alpert, Ralph Metzner and others ran a series of projects involving mescaline and psilocybin now referred to as the Harvard Psilocybin Project. In the Marsh Chapel Experiment, run by a Harvard Divinity School graduate student under Leary's supervision, Boston area graduate divinity students were administered psilocybin as a part of a study designed to determine if the drug could facilitate the experience of profound religious states, and nine out of the ten divinity students reported such experiences.

Leary's espousal of LSD, originated from an entheogenic religious experience with sacred mushrooms:

"Three years ago on a sunny afternoon in the garden of a Cuernavaca villa, I ate seven of the so-called 'sacred mushrooms', which had been given me by a scientist from the University of Mexico. During the next five hours, I was whirled through an experience which could be described in many extravagant metaphors, but was above all and without question the deepest religious experience of my life. … A profound transcendent experience should leave in its wake a changed man and a changed life. Since my illumination in August 1960, I have devoted most of my energies to try to understand the revelatory potentialities of the human nervous system and to make these insights open to others. I have repeated this biochemical and (to me) sacramental ritual over fifty times personally and, almost every time, I have been awed by religious revelations as shattering as the first experience" (Weil).

At about the same time a rubber tapper José Gabriel da Costa in Porto Vehlo, Brazil inspired by his visions under the potion, began a church the UDV or União do Vegetal based on the Amazonian entheogenic brew ayahuasca, partaken by diverse tribal cultures claiming roots back to the tenth century BC. Also contemporaneous was the discovery by Calvin Stevens of ketamine, named a "dissociative anaesthetic" by the wife of Edward Domino, the first person to test it on humans after describing his amazement at seeing a person who was fully awake but "not there." It was found to be a potent hallucinogenic drug, and the effects were described as trance-like (Jansen).

However reaction to the experimental use psychedelics including LSD led by 1962 to end of the official experiments, an investigation by the Massachusetts Department of Public Health that was eventually dropped, and the firing of Leary and Alpert, ruining promising academic careers, and sending them on a mission to popularize their affects with student culture in a collision course with conventional society, encouraging the next generation to 'turn on, tune in and drop out' - in retrospect a naïve and fanciful attempt to convert a mono-phasic society (Walsh & Grob) lacking the multi-layered spiritual traditions which had enabled the ritual use of such substances for millennia in pre-Columbian cultures. At the time only mescaline and the peyote cactus were illegal, with some uncertain exceptions for the Native American church. By 1966 psilocybin had become a schedule I prohibited drug, swept along by social anxiety about LSD use, and scientific research outside animal studies came to a halt for decades.

History now embarks on the florid journey that led immediately to Ken Kesey and the Merry Pranksters, the Electric Kool-aid Acid tests, the Grateful dead singing "Dark Star" and the Beatles "Lucy in the Sky with Diamonds", and the hippie revolution of free love, all the time denounced by the authorities and treated as social mayhem by the traditional media. At Stanford in 1959, Ken Kesey had volunteered to take part in MKULTRA at the Menlo Park Veterans Hospital, where he worked as a night aide studying the effects of LSD, psilocybin, mescaline, cocaine, AMT, and DMT on people. Kesey wrote many detailed accounts of his experiences with these drugs, both during the Project MKULTRA study and in the years of private experimentation that followed.

On the basis of a few iconic cases such as Charles Manson, who was a manifest psychopathic long before his hippie debut, who had pleaded to be allowed to stay in jail at the age of 32, having spent more than half his life in institutions, the whole flower power movement was consigned to suppression echoing the suppression of the Gnostics in the witch hunts and Inquisition. Timothy Leary became a cultural whipping post for the establishment's paranoiac vendetta. Having been caught with a couple of marijuana roaches in 1965 and 1968, he appealed the 1965 offence successfully to the Supreme Court and stood for Governor

of California, inspiring the Beatles song ‘come together’ as a campaign number. However in 1970, Leary was sentenced to 20 years in prison for the 1968 possession charge but later used his psychological guile to escape. He and his wife were smuggled out of the US by the Weathermen leading to a long international manhunt, refusal by Switzerland to extradite, and eventual capture on board a US airliner in Afghanistan. On his re-incarceration he played double agent and secured early release without incurring the ire of the underground.

Fig 4: Timothy Leary, Alex and Anne Shulgin with one of his phenylethyamine molecules (Alex Grey), Albert Hofmann (Robert Venosa), Ken Kesey and the Merry Pranksters beside the freak bus, the Grateful Dead playing at Haight Ashbury.

Stanley Owsley was a sound producer for the Grateful Dead, who in September 1965 became the primary LSD supplier to Ken Kesey and the Merry Pranksters. By this time, Sandoz LSD was hard to come by. While touring the country with the Dead, Tim Scully met Stanley and claimed that they perfected a pure process. Between 1965 and 1967, Stanley produced more than 1.25 million doses of LSD moving their laboratory out of California when LSD became illegal there. They briefly made DOM or STP but ceased production when it quickly gained a bad reputation. Nick Sand was a humanities student, when he took Mescaline in 1961. He also often visited Millbrook, the communal home of Timothy Leary's League for Spiritual Discovery. During a vision quest on DMT, Sand came to believe that he should devote his life entirely to manufacturing entheogens. He became a criminal as a matter of principle and as an act of civil disobedience, because he believed he was working for a higher good.

In 1969, Nick Sand worked with Tim Scully, producing millions of doses of the Orange Sunshine LSD. Sand was a member of "a secretive group of hippie acid dealers and hashish smugglers known as the Brotherhood of Eternal Love. The purpose of the group was "the aim of transforming the world into a peaceful utopia by promoting consciousness-expanding drug experimentation through LSD. Eventually both were arrested. At his trial, Tim Scully said that his intention was to "turn on the world" and as far as LSD chemists go, "we were doing a public service." Sand relocated to Canada. For roughly twenty years, he formed the core of international LSD manufacturing, producing about 250 million doses. In 1996, he was arrested in Vancouver, Canada, where his laboratory was found with 42 grams of LSD, or roughly 200,000 moderate doses, tested above 100% pure by the government's chemists. By late 2000, he was given an early release from prison, serving just under four years.

This stark cultural division has resulted in a continuing schizoid fracture in Western society pitting forcibly protecting a supposed emancipated society from its own freedom of choice against the right to have personal transformative experiences induced by other psychotropic substances than alcohol or tobacco. Given the prodigious production of Nick Sand alone and the lack of concrete evidence of physical or manifest social harm ensuing from such widespread consumption, and the safety of psychedelics rating far below alcohol and tobacco in terms of risks, as demonstrated in fig 21, the situation is clearly irrational and socially counterproductive.

The varying names associated with these substances illustrate society’s schizoid attitude towards them. The traditional name “hallucinogen” implies ‘mind-wandering’, seeing things that aren’t there. “Psychedelic” or ‘mind manifesting’ puts a more positive spin. “Psychotomimetic” incorrectly implies mimicking psychosis - the way such substances are cited in models of schizophrenia, in contradiction to their capacity to induce integrative healing and restorative life experiences. Finally we have “entheogen” highlighting the commonly reported experience that the altered state manifests a spiritual dimension of union with divinity.
The war on drugs has led relentlessly to the rise of major marijuana, cocaine, heroin and methamphetamine trafficking on an international basis and a cultural civil war in Western society fuelled by the unquenchable appetite of the very culture seeking to repress it, and the insatiable curiosity of the taboos generated by this suppression, fuelling an endemic subterranean underground, leading on to the

euphoric dance culture of ecstasy, and with each successive banning to the diversification of a multitude of designer drugs with varied and unpredictable consequences. This is a war of attrition, filling US prisons with social casualties, with distinct racial undertones. This can end well only in the legitimization of psychotropic agents and dealing with undesirable social consequences of hard drugs as a medical problem. The alternative is the complete suppression of any agent that can mimic, or be construed to transform, or liberate consciousness from its cultural straight-jacket - clearly not a conscionable outcome.

Meanwhile many of the people formative of the most creative processes in society today admit they owe a central place in the meaning in their life's quest to entheogens. To take six examples on LSD: Francis Crick, Nobel prizewinning co-discoverer of the structure of DNA later told a fellow scientist that it was LSD, that helped him to unravel the discovery that won him the Nobel Prize (Alun Rees, Mail on Sunday 8/8/04). Kary Mullis controversial Nobel prize-winning discoverer of the polymerase chain reaction for amplifying DNA " I found it to be a mind-opening experience. It was certainly much more important than any courses I ever took. What if I had not taken LSD ever; would I have still invented PCR? I don't know. I doubt it. I seriously doubt it" (BBC Psychedelic Science). Steve Jobs said taking LSD was one of the two or three most important things he had done in his life. He said there were things about him that people who had not tried psychedelics - even people who knew him well, including his wife - could never understand" (The New York Times, 10/5/11). Alex Gray: "Twenty-five years ago I took my first dose of LSD. The experience was so rich and profound, coupled as it was with the meeting of my future wife, Allyson, that there seemed nothing more important than this revelation of infinite love and unity. Being an artist, I felt that this was the only subject worthy of my time and attention. Spiritual and visionary consciousness assumed primary importance as the focal point of my life and art. My creative process was transformed by my experience with entheogens." Stanislav Groff: "In one of my early books I suggested that the potential significance of LSD and other psychedelics for psychiatry and psychology was comparable to the value the microscope has for biology or the telescope has for astronomy. My later experience with psychedelics only confirmed this initial impression." Albert Hofmann: "When you study natural science and the miracles of creation, if you don't turn into a mystic you are not a natural scientist. I think that in human evolution it has never been as necessary to have this substance LSD. It is just a tool to turn us into what we are supposed to be."

We like to look back on previous cultures with irony at the severe taboos they instituted, such as stoning women for adultery, burning people at the stake for heresy, or throwing the early Christians to the lions for their somewhat obsessive beliefs. In retrospect, these penalties look like desperate attempts to repress natural reproductive and intellectual choices, in societies who perceive these individual freedoms as existentially threatening because the society itself is founded on false premises that leave it vulnerable unless dire measures are taken to repress such feared individual freedoms. It thus serves us well to ponder why our so-called emancipated Western society has chosen to taboo the very agents that might bring us a new understanding of the fabric of existence and our place in the universe.

"All the cultures in human history except the Western industrial civilization have held holotropic states of consciousness in great esteem. They induced them whenever they wanted to connect to their deities, other dimensions of reality, and with the forces of nature. … They spent much time and energy to develop safe and effective ways of inducing them" (Grof).

Essentially, as already noted, the problem comes down to Western society lacking any social process for deep mental exploration in a safe sheltered setting, guided by respected elders, or people who have personal experience of transformative agents, who are able to provide protective guidance to ensure a safe passage and a healing outcome. In the sophistication of modern society, this is a contradiction because this has been a common feature of human traditional peoples throughout human history.

Although Christianity is a nominally sacramental religion, centered on the Eucharist, the Christian roots of Western culture are maladapted to inner mysteries conveyed through forbidden fruit, quickly condemned as diabolical or at least false agents of insanity and decadence. The mystical path has been under siege in Christianity from the fourth century, when Athanasius repressed the Gnostic gospels in favour of the social conformity of the Catholic canon, despite reemergence of mystical traditions in the Cathars and Albigenses, the Free Spirit Movement and mystics, from Meister Eckart to Margurete Porete, who was burned at the stake for writing "Mirror to the Simple Mind". Compounding this, particularly in the US, is the role of a government whose electoral majority depends on appeasing the conservative vote, and the consequent oppressive use of the law, strongly aligned with the capitalist ideal of a mindless consumer society, like Huxley's "Brave New World", where drugs are only accepted as pacifiers of the ongoing

consumer culture, tranquillizers and anti-depressants are compulsively over-prescribed, and agents which seem to manifestly unhinge these cultural norms are perceived as existential threats.

The rapidity with which psilocybin was outlawed, without evidence of physical, or social harm, in contradiction, both to the historical evidence of long-held spiritual devotion, and ongoing experiments confirming fulfilling spiritual and religious experiences in Western subjects, shows the process to have been driven by cultural paranoia rather than the public good. The consequence has been that, in an era of very rapid scientific progress, unearthing sweeping discoveries, scientific research into entheogens in humans was consigned to oblivion. It has thus taken the work of a few researchers, including the those at the Heffter Institute in Europe, MAPS conferences, Erowid, and of course the work of Shulgin, Nichols, Stamets, Griffiths and others in the US to bring us to the point, nearly fifty years later, where the socially beneficial properties of these agents are again becoming recognized and in particular their capacity to elicit mystical experiences of long lasting value and significance years later, as reported by both the subjects and their partners and acquaintances (Griffiths et al. 2006, 2008, 2001, Szalavitz 2011a, Brown).

Although MDMA, or ecstasy, is an entactogen, and not strictly an entheogen, it has clearly become a drug of emotionally transformative ritual use, so this history would not be complete without including the story of E. The term entactogen, for any chemical agent that induces feelings of empathy and connectedness in the user, was coined by David Nichols as an alternative to empathogen, owing to the potential for improper association of the latter with negative concepts related to the Greek root "pathos" (suffering).

The tale of Ecstasy (Jennings) forms another chapter in the futility and confusion of the war on drugs. MDMA was first accidentally synthesized in Merck's laboratories in 1912, but lay forgotten until Sasha Shulgin resynthesized it in 1976. Shulgin saw it as a valuable therapeutic psychological drug and it remained largely in therapy circles until Michael Clegg, an ex-priest, who had married, and found MDMA opened the boundaries of positive emotions and empathy between people, named it “ecstasy” and came to the conviction that his “mission was to get ecstasy to the wide world”. He began to produce hundreds of thousands of ecstasy tablets and distribute them legally in Dallas Texas where an exponentially rising demand led by 1985 to him producing 500,000 tablets a month, making him the first ecstasy millionaire.

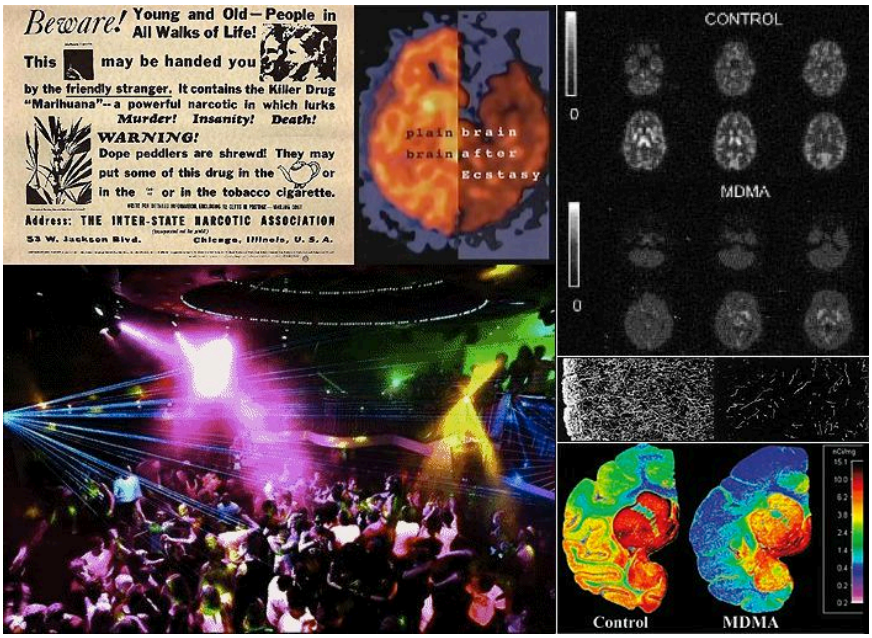


Fig 5: (Clockwise) Nothing new under the sun. Late 1930s scare marijuana poster “Murder! Insanity! Death! Late 1990s brain full of holes on ecstasy poster. Lancet study used as a basis (McCann et al). Claimed damage to serotonin Raphe pathways seven years after monkeys were dosed with MDMA (Hatzidimitriou et al). Claimed evidence of MDMA dopaminergic damage in baboons later retracted (Ricaurte et al). The trance rave has become the ritual celebration of empathy of an entire generation.

However the DEA, threatened by ecstasy's manifest lack of harm and socially positive profile, being used by relatively ordinary people rather than a bunch of weird hippies, felt it imperative to suppress the phenomenon, lest it undermine the entire attempt to treat recreational drugs as dangerous enemies of society. Ecstasy was thus, without any evidence of social harm, in 1985 classified as schedule 1, along with cocaine and heroin, ending its legitimate therapeutic use and driving its manufacture underground. A major part of ecstasy production then transferred to Europe with increasingly massive black market imports arriving back in the US.

Ecstasy became the drug of choice in the rave party scene, driven as much by ecstasy's pro-social bonhomie as by trance music and light shows. The NIDA then embarked on a public campaign to strike fear into prospective ecstasy users, by claiming that a single dose could permanently damage the brain, using a factually flawed scientific study by George Ricaurte of the Johns Hopkins School of Medicine

claiming to show vast areas of the brain of ecstasy users were full of full of holes due to loss of serotonin function. When in 2002 Ricaurte published a follow up study in Science purportedly of MDMA's effects on rodent brains, he was forced to retract it, claiming the chemical supply company had incorrectly labeled methamphetamine as MDMA, which the company overseen by the DEA denied, suggesting intentional scientific fraud on the part of the US government. When these two strategies failed, attempts were made to exaggerate the number of cases of ecstasy deaths, however James Gill, Deputy Chief Medical Examiner New York City states that of 19,000 deaths undergoing autopsy over a 3 year period, only 22 people had ecstasy in their system at the time of death and of these only 2 could be construed to have died as a result of ecstasy alone. Around 2100 people die from drug overdoses in NY in a 3 year period, around 20% of which are due to paracetamol, dwarfing the ecstasy deaths. Given the fact that, according to the DEA up to 110 million doses of ecstasy were consumed in the NY area during this time, these claims also have to be seen as part of a campaign of disinformation. Nevertheless MDMA has been found to be neurotoxic in rodents and there is some evidence of long-term effects in humans, which we will examine in due course.

2: The Enigma of Subjective Consciousness

Part of the reason psychedelic entheogens pose such a paradox for Western society is that, although we have decoded the human genome, come close to discovering the theory of everything describing the fundamental forces of nature and the cosmological process, and become a global society driven by digital computer technology, with the powers of nuclear self-destruction and global impact on the biosphere, the nature and origin of subjective consciousness remains an unresolved abyss in the scientific description.

This leads to the so-called 'hard problem in consciousness research' (Chalmers) - the fact that conscious qualia and other attributes of subjective experience are so fundamentally and qualitatively different from the objects and processes of the objective description that no brain processes such as electrical activity associated with cognitive processes in the gamma band (Crich & Koch), or conceptual models such as multiple drafts (Dennett), can form an adequate explanation. The best we can do is link coherent excitations in the global workspace with conscious processes as opposed to the incoherent unconscious processing of different brain regions (multiple references under Consciousness and Global Workspace).

Although the scientific description tells us the world around us is made out of molecular matter and that we as biological organisms are dependent on our fragile brains to survive and remain conscious, we gain this understanding only as a consensus agreement about our subjective conscious experiences, which are our only veridical access to the physical universe, from birth to death. Although brain science sees subjective experience as merely an internal model of reality constructed by the brain, it is actually through our subjective consciousness that we build up our consensual description of the physical world, both in early childhood and through learning scientific ideas of the natural world, so in this sense, subjective experience is primary and the physical world is inferred. Moreover the existential status of internal experiences, from dreaming REM sleep to meditative and visionary experiences, remains undetermined. From the subjective point of view, dreams can be as real and rich as waking experiences, and their explanation purely in terms of memory consolidation processes remains ambiguous.

This suggests that the subjective and objective aspects of existential reality might be complementary. The tantric origin says precisely this - that the existential origin lies in intimate coital fusion of subject and object, which in their retreat from union become the subjective conscious mind (Shiva) dancing the dance of Maya or illusion, in which the cosmic consciousness of the observer becomes lost in the manifold phenomena of the objective world (Shakti), perceived by individual sentient beings. Likewise the Tao is a complementarity between creative and receptive Yang and Yin principles in nature. The quantum description of the physical universe is similarly founded on complementary wave-particles, leading to a series of other complementarities, such as between matter-forming fermions and force-bearing bosons.

Current cultural perspectives on existential reality remain in a schizophrenic state between a purely materialistic perspective and religious cosmologies inconsistent with physical reality. The materialistic view is that we are simply chemical machines, that subjective consciousness is just an internal model of reality constructed by the biological computer of the brain, that mind is an illusion which can have no effect on matter and that all human action is no more and no less than a complex mechanism. If we took this description at face value, there would be no point in life, no meaning in existence, and the simplest act of voluntarily deciding to go for a walk in the park would be a catatonic delusion, for in the harsh light of reality, our conscious minds would have no control over our physical bodies.

At the other extreme religious people believe that the universe was created in seven days by God producing the plants before the Sun and Moon, that flawed nature is going to be discard in the Rapture, where we are all going to be assigned to a heavenly life in the skies, or condemned to eternal hell-fire and damnation amid visions of feathery-winged angels and the intimate presence of God in the form of an ancient man with white hair. This is clearly a mentally driven-description, consistent only with a naïve flat-Earth view of the heavens as great domes in which the stars are set, while we know the upper atmosphere is a vacuum, and there is no place for the heavenly host in intergalactic space. Looked at with any integrity we can see that all religious visions, from Genesis to Revelation, are imaginative mental fantasies of the subjective mind, coming from dreams, prophecies and visionary states.

In reality neither of these descriptions are remotely adequate and Western society stands at a cross-roads, where the central enigma of existence is still a complete conundrum pivotal to our understanding of who we are, what we are doing on the planet and how to care for an ever more fragile biosphere and protect the diversity of life and the future generations of humanity from extinction due to our own lack of foresight.

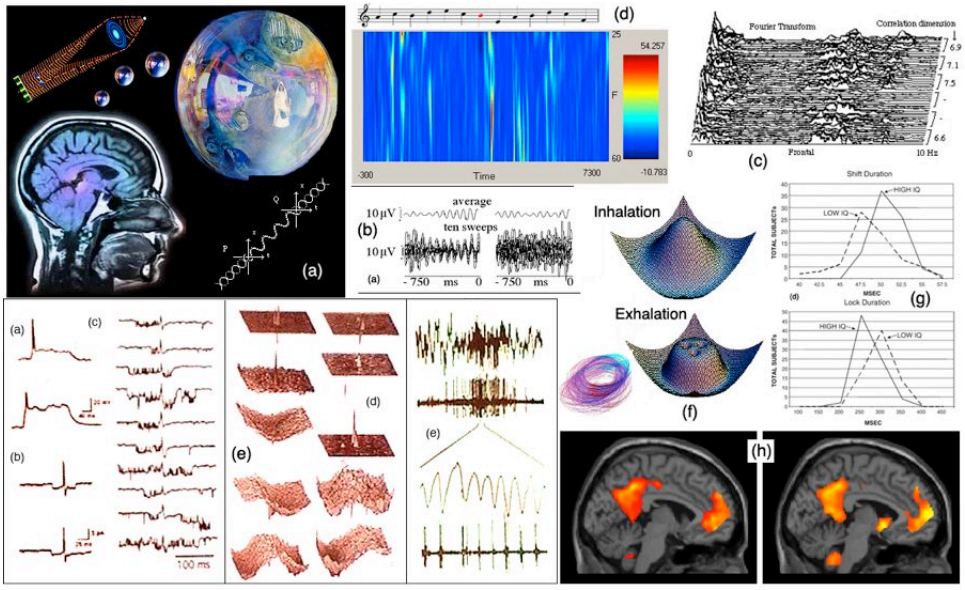


Fig 6: (a) The existential nature of subjective experience and its relationship with autonomous will remains unresolved. It's anticipatory properties could be a manifestation of quantum properties, here illustrated by the Wheeler delayed choice experiment and the transactional interpretation of quantum mechanics. (b) responses gain wave coherence (left) when their temporal occurrence becomes anticipated (Basar et al). (c) The eeg consists of broad-spectrum oscillations characteristic on non-linear chaos, also manifest (d) in active brain states such as recognizing an odd note in the wavelet transform frequency profile (King ROC). (e) Discrete change at an ion-channel can excite a hippocampal cell which in turn can result in cortical excitations through stochastic resonance (Liljenström & Uno). (f) Freeman's model of learning through chaotic excitations forming new strange attractors (Skarda & Freeman, Freeman). (g) High IQ is associated positively with phase shift durations and negatively with phase lock duration consistent with phase coherence and transitions involving disordered intermediates (Jung-Beeman). (h) Brain states involving envisaging future situations are almost indistinguishable from those dealing with past memories suggesting the brain is organized to deal with past and future using a single space-time process (Addis et al, see also Marshall, Hassabis et al, Szpunar et al).

We can gain hints of a possible solution to this existential dilemma by looking more closely at the evolutionary process and at the relation between quantum mechanics and the neurodynamic brain. Firstly the quantum universe is not a deterministic mechanism. Quantum uncertainty means many fundamental processes, such as Schrodinger's cat experiment are unpredictable. Many physicists interested in the mind-brain problem have pointed out the quantum uncertainty could in-principle provide a causal loophole making it possible for conscious mental states to influence a critically poised brain state without physical contradiction. Many processes in neurodynamics, including self-organized criticality, chaotic sensitivity and stochastic resonance show that critically-poised brain states can have tipping points triggered by a single cell, synapse of ion channel, demonstrating quantum events could indeed influence whole brain states. Chandelier cells have been shown to have such recruiting properties (Molnar et al, Woodruff & Yuste).

Notably, although pyramidal neurons have pulse-coded action potential intensities, pattern discrimination in the cerebral cortex depends not on discrete digital signals, but broad spectrum wave fronts, whose phase coherence distinguishes an attended stimulus or attended process from the ground swell of extraneous stimuli. Global phase coherence of excitations across cortical regions is also the basis of the most plausible current idea of how conscious brain states differ from unconscious peripheral processing. Phase coherence of the wave function is precisely the process underlying quantum dynamics as well, since the uncertainty relation between energy and frequency is derived from counting wave fronts.

To understand subjective consciousness it is fruitful to consider how it evolved in biological organisms. Neurosystems are not just electro-dynamic systems but heavily dependent on chemical neurotransmitters. Many of these molecules go back to the first single-celled organisms. Serotonin, our pivotal example for entheogens, has a very early origin with photosynthesis, where the indole group of tryptophan is the receptor of excited electrons. Serotonin and melatonin thus emerge as signalling molecules as soon as bacterial photosynthetic processes provided oxidation potential (Azmitia in Müller & Jacobs) and may have become ubiquitous through horizontal gene transfer (Iyer et al). At another extreme, immune reactions to soil bacteria appear to be able to induce an antidepressant effect in the prefrontal cortex through serotonin emission at the Raphe nuclei (Lowry et al). The hepta-helical protein family, common to G-protein linked serotonin receptors and many other neurotransmitters, as well as the rhodopsin of the eye, although one of the most sophisticated and diverse receptor types, occupying two percent of the human coding genome, is also one of the earliest to appear in evolution (Azmitia in Müller & Jacobs).

This evolutionary picture means that most of the critical features of both electrochemical excitation, and biochemical modulation, were already in place in excitable single eucaryote cells, in providing them with complex and diverse responses to their environment. One can see this in the neural nets of coelenterates, such as hydra, which has twelve distinct modes of locomotion, where it is not the structured organization of the nervous system which provides for complex behaviour, as there is only a disordered primitive net, which can reassemble along with the entire organism if it is turned inside out, but the dynamic sophistication of the individual neural cells (King 2008).

This picture addresses one fallacy, coming from the artificial intelligence school of thought, that the brain is just a very complex sophisticated computer, which, given the right kind of firmware and software design, could be replicated in principle by a digital computer thus showing consciousness is only a question of computer design. There are several reasons why this is in fundamental conflict with the way the brain evolved. Most, if not all, environmental decision-making problems are computationally intractable and prone to exponential runaway, like the travelling salesman problem, because the complexity of the computation grows super-exponentially with the factorial of the number of incident factors involved. The gazelle can't afford to wait at the cross roads until its computer solves each survival issue or it will surely get jumped by the tiger without ever having made the decision, so the brain has to find a way to make real time decisions regardless of classical complexity.

The brain appears to have solved this problem by utilizing massively parallel processing rather than a set of serial processors with only nominal parallel capacity. However parallel processing is not naturally suited to digital signalling because the traffic management problem of parallel threads becomes unmanageable. To avoid this, the brain appears to use a combination of wave front coherence processing and chaotic sensitivity. Wavefront coherence is ideally suited to parallel processing in precisely the way a hologram is, the wave fronts can be continuously superimposed and only the phase-coherent ones will reinforce. Dynamically this spatial superposition is complemented by non-linear temporal dynamics, which provides for sensitively-dependent transitions in and out of chaos, enabling the dynamics to remain critically tuned to its own self-organized criticality.

This brings us to an even deeper problem complementing subjective consciousness, that of intentional or 'free' will. All our ideas of personal accountability, and the rule of law and religious guilt, let alone our sense of sanity and personal autonomy, hinge around the notion that we can make conscious decisions about the physical world. Yet science tends to argue that this is an illusion and that we are really helpless victims of our brain state. Hence genetic predispositions have become commonplace defence arguments against criminal culpability.

However many of the environmental decisions our gazelle must make do not depend on determining factors, but on unrevealed contingencies, events yet to happen, and on situations where several choices might all lead to viable outcomes, something akin to collapsing the wave function of Schrodinger's cat in the quantum description. There may be a lion on the mountain path and a tiger on the jungle path, or neither today. What matters is anticipation, and it is here that subjective consciousness is tuned to do two things, firstly to give an immediate hunch which path to take, and secondly to be acutely sensitive in an anticipatory way to existential threats that may be about to strike as the gazelle goes to the water hole.

This gives us a much clearer idea of why the blind watchmaker of evolution arrived at the sappy biochemical conscious brain, rather than a blue gene super-digital computer. And why, despite having 10^{11}

neurons and 10^{15} synaptic junctions, the human brain is a lousy computer, no better than a cheap pocket calculator. The brain is not a computer at all, but a real-time space-time anticipator using chaotic sensitivity, wave super-positions and quantum entanglement to anticipate reality, by setting up dynamically unstable global brain states limiting in effective cat paradox experiments, possibly utilizing unusual aspects of quantum reality in the process. Quantum theories including quantum electrodynamics are time-reversible and examples, from the Wheeler delayed-choice experiment, to many manifestations of quantum entanglement and the handshaking processes in the transactional interpretation, illustrate 'spooky' potentialities spanning space and time.

Intriguingly recent brain scan studies have shown the cortical regions excited by looking into the future to be virtually identical to those involved in memorizing the past (Addis et al, Marshall, Szpunar et al) and damage to episodic memory structures also prevents subjects being able to envisage future events (Hassabis et al), suggesting the way the brain is going about this is in a sense 'time symmetric'. This raises all manner of to be elucidated questions about the anticipatory capacity of subjective consciousness, including reports and studies of precognitive dreaming (Dunne).

3: Fathoming the Mind-Brain Relationship and Experiential Modalities

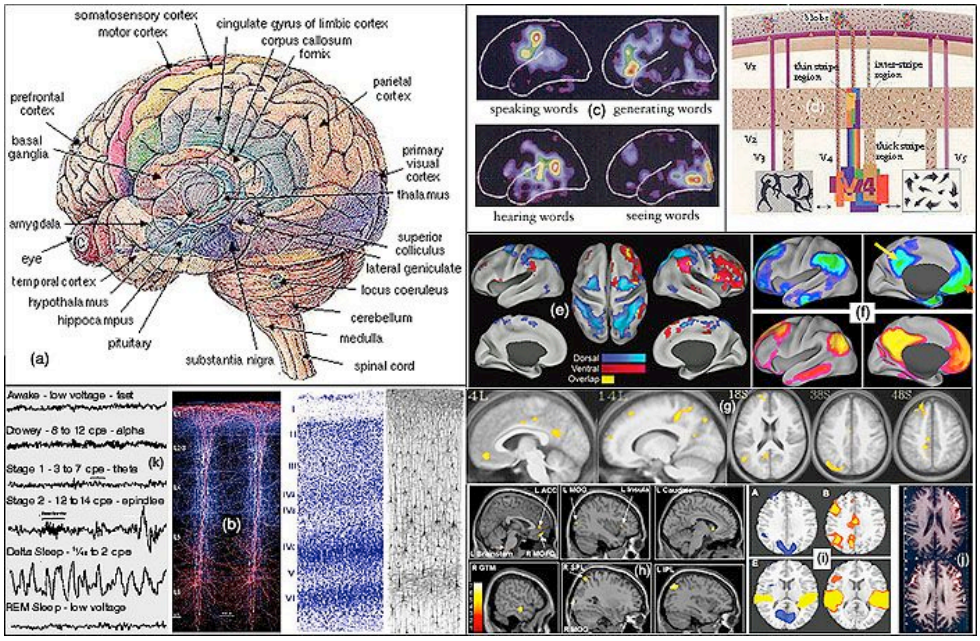
Both electrodynamic magnetodyamic EEG and MEG investigations and metabolic PET and fMRI scans utilizing radioactive metabolites and nuclear magnetic resonance have provided windows on the active brain in live subjects which give us a much clearer idea of how brain processes correspond to conscious experience. The former have good temporal but low spatial resolution while the latter are slow in time evolution but spatially more precise.

The mammalian brain is dominated by the cerebral cortices, a wrinkled pair of envelopes of neural tissue forming a sheet about a quarter of a metre in area populated by some 10^{11} neurons in five to six distinct layers, consisting of excitatory pyramidal cells mediating the output, innervated by a variety of inhibitory and excitatory inter-neurons, the 'grey' matter, with different regions connected by bundles of axon fibres, the 'white' matter connecting different cortical regions, including traversing the two hemispheres, in a massive conduit called the corpus callosum. Each pyramidal cell has dendrites permeating all the layers, with up to 10^4 incoming excitatory and inhibitory synaptic junctions involving a spectrum of distinct neurotransmitters. It is believed the cortex is organized into around 10^8 mini-columns each consisting of 50-100 neurons responding to one common feature. It is believed that the basis of the EEG's brain waves consists of resonant excitatory and inhibitory circuits in the cortex, and that fast oscillatory activity in the gamma band 30-80 Hz may correspond to active cognitive processes.

With the exception of olfaction, which has direct input through the olfactory bulbs, sensory input to the cortex and output from it, pass through a series of ganglia in the thalamus. Excitation of the cortex is maintained both by active loops between the thalamus and cortex, and by a series of basal brain centres including the Reticular Activating System, and centres mediating specific neurotransmitters, including the Raphe nuclei, and Locus coeruleus, mediating ascending serotonin and nor-adrenaline (nor-epinephrine) pathways which fan out widely across the cortex, entering specific layers to modulate excitatory tone and mediate conscious arousal and the cycles of REM and non-REM sleep. A similar dopamine pathway fans out into the frontal cortex to do with reward. An intriguing slant on the complex role of serotonin in mood is that knockout mice lacking tryptophan hydroxylase 2 which cannot synthesize serotonin, lack all sexual selection in mating, which is reversed by supplementing with 5-hydroxytryptophan (Liu et al). In addition there are loops of activity running from the cortex to the striatum and basal ganglia, to the thalamus and back to the cortex - the CSTC loop, involved in learned motor activities such as piano playing, which also play a role in learned cognitive behavior and can be disrupted by Parkinson's and Huntingdon's diseases. Another loop runs through the cerebellum, to do with bodily balance and finely-timed movement, which also plays a role in finely-timed cognition.

The regions of the cortex broadly form a mathematical transform akin to a hologram (Pribram), consisting of a set of sensory and abstract features defining each subjective experience. Thus each experience consists of multiple features and each feature can be associated with multiple experiences. There is thus no specific cortical centre associated with consciousness and the best correspondence that can be made between conscious thought, as opposed to subconscious processing, is that conscious processing corresponds to globally coherent excitations channelled through the major attention networks, as opposed to regional processing which is 'out of phase with major global processes but might come to contribute to them with the changing brain state.

Fig 7: **(a)** The human brain outlining cortical areas, as well as underlying structures including the thalamus and limbic system, including the hippocampus processing long term episodic memory and the amygdala dealing with multi-sensory reactions to flight and fight survival and basal brain structures, including the Raphe nuclei and Locus coeruleus involved in sleep wakefulness cycles. **(b)** The cortex consists of up to six layers of neurons in which pyramidal cells provide the excitatory output from one region to another while inhibitory and excitatory inter-neurons provide lateral inhibition and feedback. The 10^{11} cells in the cortex are believed to be organized into around 10^{8} mini-columns each processing a single feature. The cortex is dynamically organized into functional regions processing features of experience in massively parallel 'computation' here illustrated in verbal tasks **(c)** involving Broca's vocal expression and Wernicke's semantic interpretation areas and parallel processing of visual features **(d)** e.g. of colour and motion. **(e)** There are believed to be two attention systems in the human brain (Fox et al.) a bilateral dorsal attention system (blue) involved in top-down orienting of attention and a right-lateralized ventral attention system (red) involved in reorienting attention in response to salient sensory stimuli which occupies location in the right hemisphere somewhat complementary to the left hemisphere language areas, although the language areas tend to be more bilateral in females, who also show differences in the balance of focal and salient attention responses to crisis. **(f)** A third network has also been associated with mental activity not tied to the immediate stimuli loosely entitled the default circuit, or default network (Raichle et al, Raichle & Snyder, Mason et al, Fox D, Horovitz et al, Buckner et al), because it was found to have decreased activity when attending a sensory task (above) while the same areas become active when resting, following a stream of thought, or daydreaming. This is believed to be involved in rehearsing future scenarios (Marshall) to aid survival. Different forms of meditation display structured forms of control of the attention process and brain activation. **(g)** Zen meditation studies (Pagnoni et al, Ritskes et al) in which subjects are asked to switch from a verbal task to contemplation show transient activity consistent with the default circuit which is more quickly suppressed by experienced meditators more effectively inhibiting verbal thought. **(h)** Carmelite nuns entering oneness with God show fMRI activations in areas in very specific frontal, parietal, temporal and basal areas consistent with directed control (Beauregard & Paquette). **(i)** Likewise Tibetan Buddhists performing compassion meditation for other people's suffering show specific activation in limbic regions including cingulate cortex and insula, consistent with an empathic response to another's pain (Lutz et al 2008). (j) Sex differences in language areas (Shaywitz et al).



A good idea of the way features are mapped across the cortex can be gleaned from examining the major cortical areas. The rear occipital cortex contains primary visual areas responding to lines of a given orientation, and with increasing abstraction, more abstract features such as human faces, facial expressions, and as we move forward across the parietal lobe, spatial relationships, such as finding one's way through the city. Colour and motion are processed in parallel in complementary regions and over twenty different visual areas have been identified dealing with different visual aspects.

Where the parietal deals with spatial relationships, where things are, the temporal deals with what they are. Hearing is processed to either side of each cortex in the temporal lobes, which also have major functions in representing temporal processes like melodies, semantic memory, and associating a given situation, with a variety of others sharing abstract features with the current one. Many features of hearing, such as melody, pitch and rhythm are processed in parallel in different areas, although the primary auditory cortex is believed to have a tonotopic map similar to the line detectors of the visual system. Separating frontal areas of the cortex from the parietal is the deep fold of the Sylvian fissure. To the rear of this is the somato-sensory cortex with a map of the bodily areas, complementing our visual experience of the outside world with our tactile sensations of ourselves. To the frontal side of the fissure we have a corresponding motor map of musculature and bodily actions. As we move further forward into the prefrontal cortex we have increasingly abstract features of action, consisting of how we apply focussing

attention to control our thought processes, and our idea of our active goals and what we want to achieve in life. Many specific prefrontal areas governing forms of executive control have been elucidated from studies of the effects of damage to these areas. Some prefrontal areas affect cognitive control of attention while others such as the orbito-frontal leave intellect and IQ unaffected but disrupt the person's capacity to make realistic emotional life decisions. The region around the principal sulcus of the frontal lobes contains both an active representation of the visual field, enabling working memory to anticipate actions in time, and a representation of what these things are, forming a complementary relationship with parietal and temporal regions in working memory (Kandel et al). We can thus envisage conscious thought processes in terms of a 'global workspace' consisting of major feedback resonances between the frontal cortex and the temporal and parietal mediating the spatial and temporal aspects of the ongoing decision-making process.

On the inner side of the cortical sheet facing the centre plane is the cingulate cortex, dealing with emotional representations. This is also connected with the extreme of the temporal lobe and two other centres on the periphery of the cortical sheet, the amygdala and hippocampus in a global feedback loop loosely entitled the 'limbic system', associated with emotional dynamics. The amygdala has a role in integrating sensory experiences in relation to flight and fight survival and the hippocampus has a pivotal role in laying down experiences into sequential memory. Temporal lobe epilepsy can give rise to complex orchestrated experiences, some of which can be given a quasi-mystical status by the subject. This caused the neuroscientist Ramachandran to suggest that Temporal lobe excitation carrying across to the amygdala could be the basis of religious experiences of emotional exaltation combined with overwhelming significance - the so-called "God spot". At the least this gives an interesting interpretation of religious fervour as an idiopathic brain state (Ramachandran & Blakeslee, Persinger, Bielo).

Several key processes, including language, are believed to be lateralized, enabling the two cortices to have complementary functions. For example, language meaning is processed in the left temporal Wernicke's area and fluent execution in the left frontal Broca's area, although women often appear to have a more bilateral processing of language, in which right hemisphere activity might be associated with creative use of language. Due partly to some intriguing experiments in which the corpus callosum of intractable epileptics has been severed, the concept of lateralization has led to some fanciful concepts with only partial validity, stylizing the left hemisphere connected to the right hand with structured organized processing and the elusive right hemisphere with intuitive and creative processing.

Consistent with this view, two opposing global attention systems have been identified, one the dorsal attention network deals with focal attention in the global workspace and is bilateral connecting areas such as the frontal eye fields to parietal and other areas. Complementing this is the ventral attention network whose role is to bring in salient stimuli, important to the subject, from the periphery. Intriguingly this has lateralized activity in the right cortex, complementing the left hemisphere regions traditionally associated with language, lending support to the above model of lateralization. A third system connecting the frontal anterior insula and the anterior cingulate, involving fast-transmitting von Economo neurons, may mediate integrated bodily interoception, emotional and cognitive awareness and timed framing of the immediate present, forming a central process of self-consciousness (Allman et al, Cauda et al, Craig, Williams C).

A fourth system, the 'default network', is associated with mental activity not grounded to any immediate activity. It was first discovered because there were areas with enigmatic deactivation in a variety of brain studies. When subjects were then tested just resting or daydreaming the same areas were activated. The default circuit is activated by processes as diverse as autobiographical memory, envisioning the future, theory of mind, moral decision-making (Buckner et al, Mason et al, Raichle M. & Snyder), as well as mind-wandering activities such as daydreaming and worrying. The default circuit is believed to be a state in which we aid our survival strategies by using down time to rehearse impending situations of significance to enhance our ability to cope with them successfully. It has also been associated with improved creative thinking over focussed working memory, for example in solving counter-intuitive puzzles (Christoff et al).

Dreaming, or REM sleep remains an enigmatic and life-shaping aspect of subjective experience whose physiological and experiential status remains unresolved. Sleep begins with shorts EEG bursts called sleep spindles interrupting waking EEG and enters a series of cycles, in which waves of deep slow wave SWS sleep alternate with rapid eye movement REM or dreaming sleep. During phasic REM bursts, separated by tonic REM where there is residual alertness the cortex has an EEG similar to the waking state, with pronounced thalamo-cortical activity (Wehrle et al), and the body, except for the eyes, is effectively paralysed by a filter in the basal brain. The cycles of deep sleep are driven by synchronous burst firing in the thalamus interrupting the low voltage asynchronous passage of information to the cortex,

associated with the activity of waking and REM sleep. Sleep cycles, although they appear to occur widely across the animal kingdom from arthropods (Shaw et al, Hendricks et al) to vertebrates (Hobson), vary a great deal among mammals with different circadian habits (Siegel 2001, 2005, 2008). The sleep cycle, like the default network, has been associated with aiding the brain in forming better responses to strategically stressful situations plaguing waking life. Although the REM state is similar to waking EEG, fMRI and PET scans show reduction of prefrontal activity and heightened activity in visual areas, as shown in fig 11.

Both REM and non-REM sleep have been associated with memory re-encoding and consolidation. Non-declarative aspects of memory, from solving the towers of Hanoi to physically manipulating an unstable object, show significant improvements from the learned plateau with specific sleep phases, from REM, through light stage 2, to deep SWS sleep. Episodic memories are thought to consist of multiple hippocampally linked memory traces located within neocortical regions and dependent on the hippocampus for their integrated recall, Cycles of SWS and REM sleep appear to be associated with re-encoding of emotionally significant memories, with information passing between the hippocampus holding space-time indices of significant recent experiences into long term optimized form in the prefrontal cortex. Hippocampal activity is enhanced over other activity in REM as against both waking and non-REM sleep, while the dorsolateral prefrontal cortex, involved in decision-making and memory, becomes further inactivated. Low cortisol and reduced reticular acetyl-choline activation early in sleep favours cycles of deep SWS, with cortisol rising slowly over the night, as periods of REM sleep become more accentuated. Studies have detected replays of spatial tasks in the hippocampus, time-compressed in SWS, and then in REM. REM is also believed to enhance synaptic plasticity resulting from adapting to novel environments, enhancing the adaptive response (Payne & Nadel, Stickgold, Stickgold et al, Maquet et al, Nielsen).

These cycles are mediated by reciprocal changes in activation between the reticular activating acetyl-choline system and serotonin, nor-adrenaline and dopamine pathways fanning out across the cortex from the hypothalamus and basal brain nuclei (Saper et al). In REM, the Raphe nucleus serotonin and Locus coeruleus nor-adrenaline pathways mediating cortical responsiveness and arousal in the waking state are silent, while there is reticular activation of acetyl-choline pathways, in excess of the waking state and an EEG similar to waking, rather than the light sleep spindles, or slow waves of deep sleep.

Memory processing may be consistent with many of the experiential features of dreaming, such as bizarre content, which may appear to mix features of many experiences, and dreams being perceived as direct experiences in the present, often having emotionally charged character. Although dreams can be hard to remember, and episodic memory is idiosyncratic, dreams and particularly intense nightmares, can have substantial episodal content. Furthermore a person can often retrogressively remember quite long sequences of dream episodes on lying still on waking from a dream provided the weird disconnections plaguing dreaming experience can be negotiated. Brain scans of REM sleep show strong activations of perceptual, e.g. visual areas, while the prefrontal cortex has reduced activity consistent with the relative difficulty we have controlling the direction of our dreams and also with the memory consolidation model.

Dreams can have a very rich existential status, often as convincing to the experiencer as waking life, making it hard to give oneself criteria to distinguish dream from reality, for example to endeavour to enter a lucid dreaming state. The existential status of dreaming experience remains undetermined, along with any perceived implications for subconscious discovery or prophetic precognitive hunches. Although dreaming reality may be just a manifestation of memory processing, just as waking life may be just an internal model of reality constructed by the brain, the existential nature of dreaming experience remains a challenging and very different realm from waking experience, whose potentialities remain to be fully explored.

By contrast with the rich and bizarre nature of dreaming, mental states associated with prayer and meditation tend to involve focused control and suppression of the wandering mind through limiting the verbal thought process, or focussing on a spot. While these mental states are highly varied, they share common features of intentional control of the mental process. Zen meditators in fMRI studies show more rapid and complete suppression of the mind-wandering of the default network (Pagnoni et al), with increased activity in the prefrontal cortex and basal ganglia and decreased activity in the occipital (visual) cortex and anterior cingulate processing emotion (Ritskes et al). In EEG studies they showed a significant increase in frontal alpha and occipital beta power, whereas an average increase of theta power was observed in controls indicating loss of concentration (Huang et al). Consistent with one-pointed concentration, Zen meditators recalled more subliminal messages than controls (Strick et al).

Tibetan Buddhist meditators in PET and fMRI studies have increased blood flow in the cingulate, inferior and orbital frontal cortex, dorsolateral prefrontal cortex and thalamus (Newberg et al 2001, Hanky). EEG studies show greater activation in attentional regions, including fronto-parietal, cerebellar, temporal, para-hippocampal, and posterior occipital, possibly due to the attended dot (Brefczynski-Lewis et al). They have also been found to enter high-amplitude gamma-band oscillations with high phase-synchrony during meditation, consistent with a one-pointed concentration with heightened attention (Lutz et al 2004). By contrast, compassion meditators under PET show similar activations to a person feeling empathy for a person in pain (Lutz et al 2008). In a more recent fMRI study contrasting "focused-based" and "breath-based" practice. In the first, blood flow increased in the medial prefrontal cortex and left caudate, but decreased in parietal and occipital regions. The second induced activation in several limbic structures and the left superior temporal cortex (Wang et al).

Investigation of Transcendental meditators by PET (Newberg et al 2006b) also found bilateral prefrontal activation associated with relaxed attention on the mantra, other increases in frontal, occipital and parietal areas and a decrease in the thalamus and hippocampus. An fMRI study centered on the capacity of the relaxed state to be helpful in dealing with an induced painful stimulus saw reductions in the prefrontal cortex, anterior cingulate cortex, and thalamus (Orme-Johnson et al), and has been suggested to be linked to hormonally induced increases in GABA (Elias et al). Catholics observing a Marian image saw increases in the ventrolateral prefrontal cortex and brain stem leading up to the thalamus (Wiech et al).

Brain studies of Carmelite (Beauregard & Paquette) and Franciscan nuns (Bielo) in professed 'union with god', which they admitted was difficult to achieve in a noisy MRI tunnel, show different structured activations, with increased activity in the caudate nucleus associated with learning, memory and falling in love, the insula processing body sensations and social emotions, the inferior parietal processing spatial awareness in contradiction to the Zen studies, the medial orbito-frontal and prefrontal cortices dealing with emotional and executive decision-making, and the middle of the temporal lobe. Most prevalent brain waves were long, slow alpha waves such as those produced by sleep, consistent with a relaxed state. By contrast with the prefrontal control evidenced in Buddhist meditation, during speaking in tongues, by Christian women who had practiced glossolalia for more than 5 years, there was a decreased blood flow in the frontal lobes bilaterally and in the left caudate, indicating relaxation of executive controls (Newberg et al. 2006a).

In comparing these highly varied and contradictory results, one can conclude that claimed states of higher spirituality are varied products of different forms of concentration, which share the feature of overall focused control, but otherwise look like distinct humanly-generated states of mind, rather than convergence on the 'divine'. One needs to consider the possibility that the profound transformations of the cortical dynamic induced both by dreaming and by entheogens may give rise to deeper potential for exploratory existential processes, which might nevertheless be enhanced by contemplative repose.

4: Doors of Perception: Classic Psychedelics and Serotonin Receptor Agonists

In fig 8 are shown a selection of the classic psychedelic entheogens, along with MDMA and methamphetamine for comparision and salvinorin and Ketamine which have different action but entheogenic reputations. Although many of are phenylethylamines, rather than indoles like serotonin, and might be more expected to act on the nor-adrenalin receptor, they have been shown to exert their psychedelic action through a common pathway, via serotonin receptors (Lyon et al), and in particular 5HT2a (Ray), because competitive 2a antagonists, such as ketanserin, block psychedelic activity and mice genetically engineered to lack 5HT2a receptors lose the psychedelic head-twitching response (González-Maeso et al 2007). Molecular QSAR studies have also been made (Clare, Schulze-Alexandru, Thakur).

The tryptamine psychedelics are agonists for 2a, 2c and 1a. Broadly speaking 2a seems to produce the kaleidoscopic visionary effects, 2c a degree of anxiety and disordered thought, and 1a shuts down the Raphe serotonin secreting nuclei, causing a dream-like effect. The 2c receptor is X-linked, so polymorphisms can affect the sexes differently. Splicing appears to be regulated by the small nucleolar RNA SNORD115. Phenylethylamines act on 2a and 2c (Moya et al), although all agents act on multiple receptors (fig 8 right). LSD remains an enigma to this day because it is only a weak partial agonist of 2a and has diverse effects on a variety of receptors (see figs 8 and 14), including the above, which provides no explanation why it is so potent. 13-OH-LSD, a potent major metabolite, may induce dopamine related paranoia late in an LSD trip (Nichols).

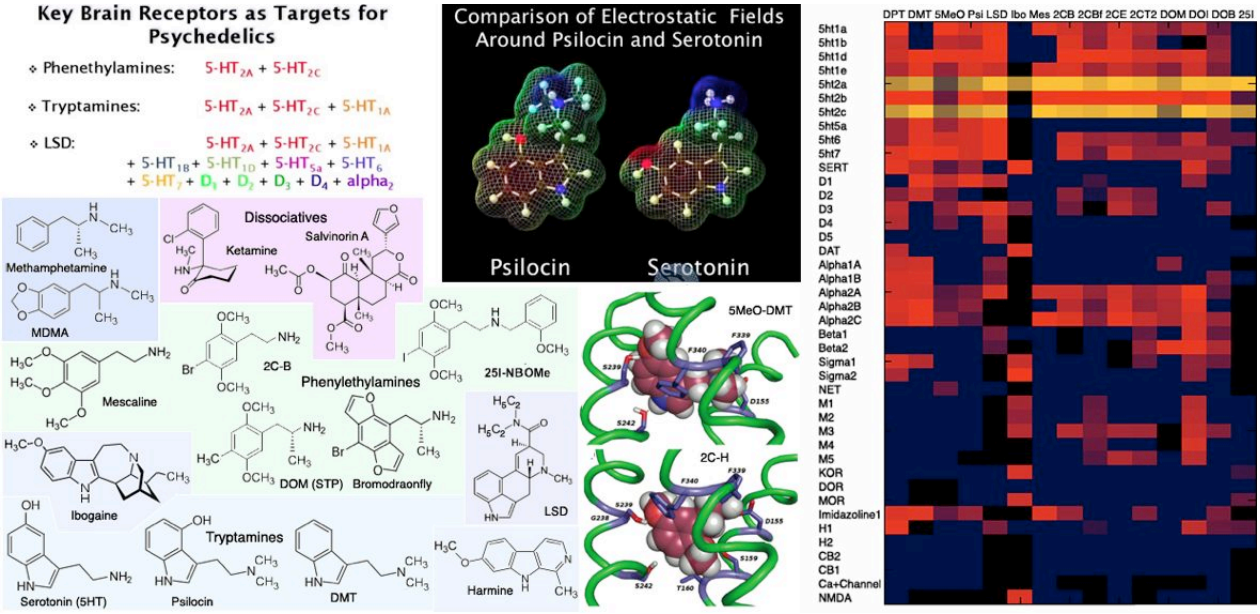


Fig 8: **(Lower left)** Classic psychedlic hallucinogens (Nichols 2004, Schultes & Hofmann) are either tryptamines (psilocin, DMT, with LSD and ibogaine as modified members, with harmine included as a monoamine-oxidase inhibitor potentiator of DMT in the Amazonian brew ayahuasca) or phenylethylamines (e,g, mescalin, DOM, 2C-B, bromodragonfly and 25I-NBOMe), which are full or partial agonists of serotonin receptors. Psychedelics are also referred to pejoratively as psychotomimetics, or hallucinogens and affirmatively as entheogens, providing long-term spiritual and psychological coherence (Griffiths et al 2006, 2008, 2011, Khamsi, Frood, Barbosa et al). Two other molecules which are referred to as entheogenic dissociative hallucinogens are ketamine and salvinorin A, which have distinct effects and act at completely different receptors, the NMDA (N-methyl d-aspartate) glutamate receptor and κ-opioid receptors respectively. The phenylethylamine derivates have been modified with a view to optimize receptor binding through appropriately located H-bonding and hydrophobic interactions. The amphetamine moiety in DOB and in addition the ring structures in Bromodragonfly result in a strongly binding super-potent molecule with slow onset and very long-lasting effects, which can be a life-threatening combination which can cause catastrophic organ and peripheral tissue damage. There may be some commonality between ketamine and the classic psychedelics through linkage between 5HT2a and glutamate mGluR2 receptors and in turn with the NMDA target of dissociatives. Ecstasy (MDMA) although it is a serotonin releasing agent, like many related serotonin uptake inhibitor antidepressants, is not a psychedelic entheogen, but rather an entactogen. Methamphetamine, which is a stimulant, rather than psychedelic, is a dopamine releasing agent, but also forms a moiety in many phenylethylamine psychedelics and MDMA. **(Lower right)** Although the phenylethylamine psychedelics, (e.g. 2C-H) more closely resemble dopamine and nor-epinephrine than the indole-based serotonin, the way they fold at the serotonin receptor (Braden, Braden & Nichols) leads to similar 5HT2a activation to the tryptamines (e.g. 5-methoxy-DMT). **(Upper left)** Key brain receptors as targets for psychedelics (Nichols 2011). While phenylethylamines affect 5HT 2a and 2b, tryptamines also affect 1a and LSD has multiple affects on several serotonin, dopamine and other receptor types leading to a complex effect. The n-benzyl phenethylamines such as 25I-NBOMe are strongly selective for the 2a receptor (Braden et al), so are experimental tools for investigating the 2a receptor. The central psychedelic effect is believed to be driven principally by 2a (Nichols & Nichols), because competitively-binding 2a antagonists such as ketanserin, and genetic modification, in animal studies (González-Maeso et al 2007), show repeatable psychedelic side-effects, such as 'head twitching', are obliterated by loss of 2a agonism. The other serotonin receptors are believed to have secondary action, with 2c contributing up to half the head twitching effect in animal studies (Canal et al). The fact that 2c antagonists are anxiolytic suggest 2c agonism may promote anxiety and ensuing disordered thought processes. Some of the initial anxiety caused by selective serotonin reuptake inhibitors, or (SSRIs is believed to be due to excessive 2c signalling. 2c is X-linked and so can have differing effects both between males and females and between individuals leading to different degrees of anxiety. Agonism of 1a in the tryptamines paradoxically silences the Raphe nucleus responsible for serotonin innervation of the cortex (Braden, Nichols 2011), as occurs in REM, or dreaming, sleep. The effects of psilocybin on 1a when 2a (& 2c) were selectively blocked with ketanserin still showed reduced attentional tracking ability, but there was no significant effect on spatial working memory under psilocybin (Carter et al). **(Upper center)** Psilocin (the active metabolite of psilocybin) and serotonin electric fields compared, showing the 4-OH and dimethyl moieties come together in psilocin to alter the charge polarities and spatial distribution (Nichols 2011). **(Right)** Heat map of normalized receptor interactions shows a wider distribution than the simplified list upper left (Ray). Activity dark blue=0 to red=4 (orange for 2a and 2c, black no data). Profiles of DPT, DMT, 5MeO-DMT, psilocin, LSD, ibogaine, mescalin, 2C-B, 2C-B-fly, 2C-E, 2C-T-2, DOM, DOI, DOB, 25INBMeO (Nicholls et al). The mescalin profile is corrected for 5HT2a,c binding using PubChem Assay (http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?cid=4076). Notice the huge spread of receptor activity in DOI compared with DOB, and the manifest difference in activity between DMT and 5MeO-DMT consistent with their different subjective effects.

Beginning with the mescaline molecule, Sasha Shulgin and others, by educated hunches, synthesized a variety of phenylethylamine variants making minor modifications to the groups around the benzene ring to bring the H-bonding and hydrophobic parts of the molecule closer in line with the side chains on the active surface of the 5HT receptor. This resulted in a series of molecules with much greater potency than mescalin. DOM, also known as STP, carrying an amphetamine methyl group, had an active dose of 3-10 mg, rather than the 400 mg of mescaline, and a duration of 14-20 hours. DOB had 1-3 mg and 18-30 hours. The 2C series without the amphetamine methyl had shorter milder activity, with a dose of 2C-B being 12-24 mg and a duration of 4-8 hrs. Cyclizing the side methoxy groups and retaining the amphetamine methyl resulted in super-potent molecules such as bromodragonfly (Nickson, Chambers et al, Schultz et al), with dangerous physical effects including seizures, gangrene, organ failure and death, particularly when confused with 2C series molecules. The active dose is around 0.2-0.8 mg and the effects last up to 72 hours, indicating very strong binding, with doses of a few mg being dangerously toxic. In 1999 the n-benzyl-phenethylamine super-potent selective 5HT2a receptor agonist class was discovered, including 25I-NBOMe (Braden et al). The dose by smoking is 0.15-0.3 mg and the duration 3-8 hours. My subjective experiences of both psilocybin and 25C-NBOMe are included in the case study.

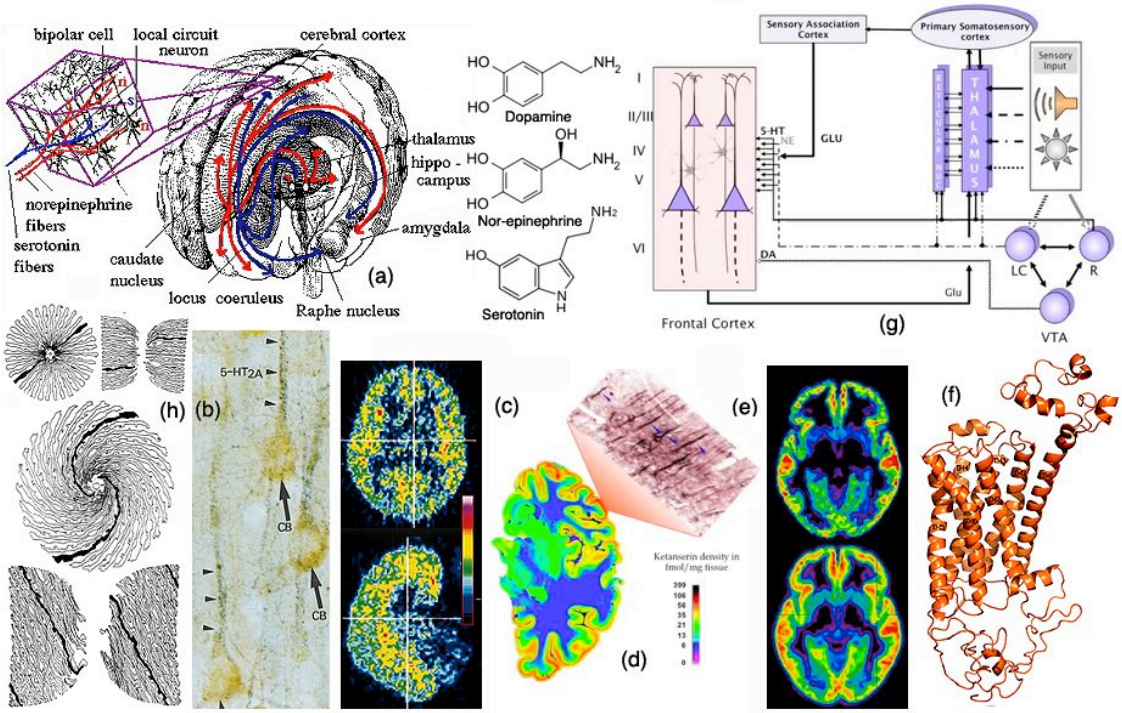


Fig 9: **(a)** Ascending pathways from the Raphe nucleus (R) and Locus coeruleus (LC) innervate wide areas of the cortex via serotonin and nor-epinephrine synapses. Dopamine pathways from the ventral tegmental area (VTA) likewise mediate dopamine synapses to areas of the cortex. Dopamine is involved in the reward system, nor-epinephrine in arousal, and serotonin in a variety of modulating effects. **(b)** 5HT 2a receptors are located on apical dendrites close to the pyramidal cell body (Jakab & Goldman-Rakic). The action of 1a and 2a receptors on pyramidal cells appears to be opposed. **(c,d)** Excitatory 5HT2a receptors are widely distributed across the cortex with significant concentrations in the frontal and visual areas. Inset shows an arrow pointing to their location on the pyramidal cell (Stein et al, Nichols 2011). **(e)** A healthy individual (below) shows greater 2a activation than a mentally 'at-risk' patient (Hurlemann R et al). **(f)** Model of the 5HT2a receptor, a hepta-helical rhodopisn-like G-protein coupled receptor (Kanagarajadurai). Rhodopsin is effectively a neuroreceptor agonised by the conversion of retinal from the 11-cis to the all-trans state by an incident photon. **(g)** Model of the possible action of psychedelics involves several possible alterations of serotonin pathways, including altering the signalling pathways of cortical pyramidal 5HT2a receptors, possibly affecting glutamate excitatory responsiveness (Muschampa et al), reducing lateral inhibition of cortical inter-neurons, leading to the ramification of patterns from cortical column to cortical column across the cortex, the shutting down of Raphe nucleus serotonin activity through 5HT1a activation, paralleling its silencing in REM dreaming and alteration of cortico-striatal-thalamo-cortical CSTC feedbacks mediated by serotonin receptors. This would also be consistent with a another model - reduction of filtering functions in the thalamus causing a sensory flood in the cortex (Nichols 2011, Scrugs et al, Vollenweider) Both glutamate excitation and thalamic models have been challenged (Béïque et al), but only using the phospholipase-C pathway (fig 10), they suggest that 5HT2a receptors 'facilitate intrinsic networks within the PFC'. **(h)** Tunnel and spiral patterns may originate from enhanced wave fronts running across the occipital cortices (Contreras, Benussi et al) due to the complex logarithmic map between the cortex and perceived visual field (Bresslof et al). This suggests that one mechanism of psychedelic activity is reduction of lateral inhibition between cortical mini-columns setting up an additional dynamical excitation to the deep white matter connections of pyramidal cells.

Work has also gone into modifications of the tryptamine psychedelics, mostly by elongating the N-dimethyl groups or adding to or shifting the 4-OH. Dimethyltryptamine, or DMT, is a short-acting highly potent psychedelic, which can be smoked, or consumed by mouth with monoamine oxidase inhibitors, such as harmaline. It occurs widely in nature and in trace amounts in the human body. 5-methoxy-DMT is more potent but has a reputation for being a near death experience lacking joy or colour. 5-hydroxy-DMT or bufotenine, which stands intermediate between serotonin (5-hydroxy-T) and psilocin (4-hydroxy-DMT), has a controversial reputation for physical affects, including cyanosis on intravenous use, but according to Ott has effects similar to DMT and psilocybin lasting about 90 minutes when taken intra-nasally, without deleterious side effects (Ott 2001). LSD remains the most potent and spectacular molecule in its class. Comparison of the electric fields around psilocin and serotonin shows how the combined effect of the OH moved to the 4 position and the N-dimethyl alter the charge distribution in the top of the receptor site in such a way as to alter the protein cascade. A variety of molecules, from LSD to 25I-NBOMe, all fit the 2a receptor in such a way as to bond to critical amino-acid side chains and elicit a psychedelic response.

In seeking an explanation for how classic psychedelics cause their profound changes of subjective consciousness, we need to understand how the critical 5HT receptors are distributed and how they modulate major brain circuits. 2a receptors are widely distributed throughout the cerebral cortex with particular concentrations in frontal and occipital areas. They have a major role in mood and sleep wakefulness cycles. Serotonin reuptake inhibitors such as Prozac have become popular anti-depressants but neither they nor serotonin, or a variety of other 5HT2a agonists are psychedelics. We thus also need to discover why some 5HT agonists are psychedelics while others such as serotonin itself are not. The serotonin receptors are G-protein linked receptors so they do not open an ion channel, but set off one or more chain reactions between proteins and other signalling molecules inside the target neuron. Current think is that psychedelic molecules are not only 5HT2a agonists but bind to the receptor in such a way as to fundamentally alter the ensuing protein cascade.

One of the major sites of 5HT2a receptors is on the apical dendrites of pyramidal cells, which are the main output neurons from a given area of the cortex, and penetrate all the cortical layers, forming up to 10,000 synapses with a variety of inter-neurons having many different types of neurotransmitter, both inhibitory and excitatory. Serononergic agonism has been found to increase excitatory post-synaptic currents in layer V pyramidal cells of prefrontal cortex, but intriguingly by an asynchronous mode of glutamate release suggesting the involvement of pre-synaptic receptors (Aghajanian & Marek). There are also receptors on the connections between the thalamus and cortex which provide the main sensory and motor pathways and a series of reciprocal connections between the two believed to be integral to maintaining a state of active consciousness and memory functions. The reticular nucleus surrounding the thalamus, which has rich serotonin receptors (Rodríguez et al). There are also serotonin receptors on cortical interneurons, whose feedback properties can also be affected by psychedelics. The serotonin receptors in the cortex are fed by an ascending neural pathway of serotonin-secreting axons from the Raphe nucleus in the basal brain that innervates wide areas of the cortex forming synapses with pyramidal neurons on their apical dendrites. However the serotonin emitting Raphe neurons also have 5HT1a receptors, which in the case of psilocin turn off the serotonin pathway.

All of these processes are possible targets for the effects of psychedelics and all of these have been invoked as possible contributors to the psychedelic state. One idea that gives some explanation of the kaleidoscopic patterning is that psychedelics modulate interneuron feedback in such a way as to allow patterns of excitation to leak from one mini-column to another thus setting off waves of excitation across the cortex, in addition to deep pyramidal connections, which could be perceived as patterns, and sounds. Perception of tunnels and spirals is consistent with such simple waves of excitation travelling across the visual cortex through the complex log transform between occipital cortex and perceived visual field. However synesthesias also suggest modulation of deeper connections between cortical areas. Another possible mechanism is the serotonin modulation of reciprocal connections between the cortex and the thalamus via the striatum, the CSTC loop (Marek et al 2000). More directly one can examine the 5HT2a receptors on pyramidal cells for mechanisms that would directly alter pyramidal excitation, possibly through connection to glutamate excitatory expression. Finally one can invoke changes to the ascending serotonin pathways. The Raphe nucleus monitors vigilance, so its silencing could result in drowsiness. Psychedelics also increase the burst firing of the locus coeruleus nor adrenaline pathways, resulting in experience of novelty and surprise. The full effects could involve any or all of these in varying combinations, as noted in fig 9(g).

Fig 10 outlines some of the prevailing ideas about how the protein cascade resulting from psychedelic receptor agonism might be altered. The 2a receptor has been found to have two immediate pathways, the central one involving phospholipase-C and the other via phospholipase-A2. Psychedelics appear to have greater differential activity on the A2 pathway, but the effect is not consistent across different psychedelics when we consider the actual potency of an agent to elicit either pathway at a given concentration. Gene studies then sought to elucidate *in vitro* gene expression differences and found a consistent activation of *egr*-2 only in psychedelics, while all 2a agonists activated *c-fos*. *Egr*-2 is further discussed in fig 12. 5HT2a receptors are also found peripherally, e.g. on blood vessels, where their activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency (Yu et al).

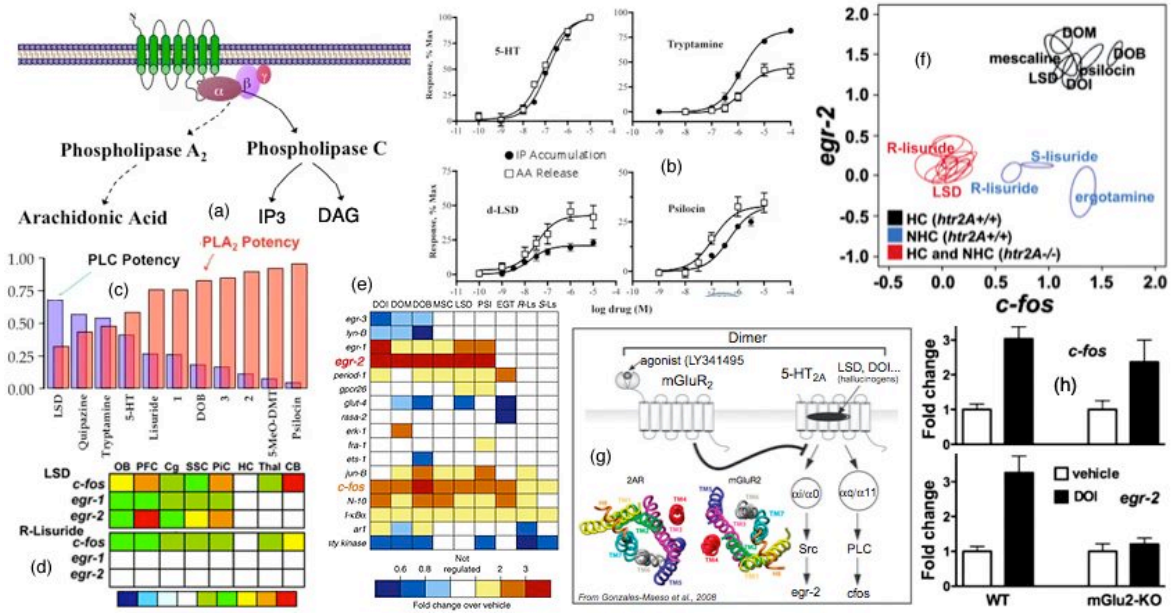


Fig 10: In seeking for an explanation of how psychedelics, such as psilocin, cause profound changes of consciousness, apparently through 5HT2a receptors, but other 2a agonists such as serotonin itself do not, interest has focused on the idea that the 2a receptor can be activated in different ways by molecules with slightly differing binding, so that the resulting G-linked protein cascades have significantly different outcomes. One area of interest **(a)** is in the differing activations of the central phospholipase-C pathway and the phospholipase-A2 pathway (Felder et al, Nichols 2011), which seems to be differentially more activated **(b)** by psychedelics, such as psilocin and LSD, but these show contradictory responses **(c)** in terms of actual potency (Nichols 2011). Note the paradoxically weak agonist effect of LSD in (b). Cox-2 (Mackowiak et al) and MAP kinase activation (Nichols & Sanders-Bush 2004, Kurrasch-Orbaugh et al) and PSD-95 (Abbas et al) have been found to be elicited by DOI and LSD. **(d,e)** In vitro and in vivo investigation of gene activations caused by receptor activation has shown a consistent differential activation of *egr*-2 (early growth response 2) a three-finger transcription factor, as opposed to *c-fos* (Nichols & Sanders-Bush 2002), with all 2a agonists promoting *c-fos*, which is rapidly upregulated by many stimulatory pathways and by action potentials, but only psychedelics (DOI, DOM, DOB Mescalin, LSD and psilocybin) promoting *egr*-2. In turn LSD vs psychedelically inactive R-Lisuride is seen to activate *egr*-2 in OB, olfactory bulb; PFC, prefrontal cortex; Cg, cingulate cortex; SSC, somatosensory cortex; PiC, piriform (olfactory) cortex; but not in HC, hippocampus; Thal, thalamus; CB, cerebellum. (Gonzalez-Maeso & Sealfon, Gonzalez-Maeso et al. 2003, 2007). This suggests a primarily cortical level of psychedelic activation. **(f)** Similar responses in 2a+/+ mice obliterated in 2a-/- knockout mice (ibid). **(g)** Serotonin agonism also appears to be linked to a pairing of 5HT2a with an adjacent glutamate mGluR2 metabotropic (G-protein-linked) receptor (ibid, Bockaert et al in Müller & Jacobs, Fribourg et al, Kondo & Sawa, Uslaner et al, Gewirtz & Marek) in which psychedelic effects such as 'head twitching' in animal studies are also abolished by the mGluR2 agonist LY379268 (Molinaro et al), or **(h)** by removal of the mGluR2 receptor altogether in knockout mice (Moreno et al 2011a), suggesting this may be a key link between serotonin and glutamate modulation of pyramidal neurons. The link is mutual and opposing. mGluR2 agonists increase the affinity of 2a for hallucinogen binding, while 2a agonists decrease the affinity of mGluR2 agonists for glutamate receptor binding (Kreuts & Carlo). Activation of G proteins by 2a was altered by co-expression of mGluR2. Induction of the gene, *egr*-2 that is selectively stimulated by hallucinogenic 2a agonists was blocked by an mGluR2 agonist, whereas induction of *c-fos*, which responds both to hallucinogenic and non-hallucinogenic 2a agonists, was unaffected by the same treatment. The heteroduplex mechanism has been contested (Delille et al) and it may just be one instance of a more general phenomenon of receptor cross-talk essential for multimodal modulation of neurotransmitter action.

An intriguing connection then emerged between the 5HT2a receptor and the G-linked glutamate receptor mGluR2. A reciprocal functional inhibition of 5HT2a agonism and mGlu2/3 agonism has been described in the prefrontal cortex of rat. In these studies, 5HT2a receptor activation induced excitatory postsynaptic currents (EPSCs) in the medial prefrontal cortex (Aghajanian & Marek), and a mGlu2/3 antagonist further

enhanced the frequency and amplitude of EPSCs (Marek et al., 2000). By contrast mGlu2/3 agonists or 5-HT2A receptor antagonists suppressed EPSCs and attenuated behavioral effects of both serotonergic hallucinogens (e.g. LSD) (Gewirtz & Marek), and dissociative anesthetics (e.g. PCP) (Moghaddam & Adams). Extensive subsequent research is discussed and illustrated in figs 10 and 12.

These two receptors may lie adjacent in the pyramidal cell membrane. Competitive agonists for the glutamate receptor abolish psychedelic effects in animal studies and they are also absent in knockout mice lacking the glutamate receptor. The link between these two receptor types is mutual, with mGluR2 agonists increasing the affinity of hallucinogens for 2a binding, whereas 2a agonists decrease the affinity of mGluR2 agonists for glutamate receptor binding. Moreover, activation of G proteins by 2a was altered by co-expression of mGluR2. Induction of *egr-2* was blocked by an mGluR2 agonist, whereas induction of *c-fos*, which responds both to hallucinogenic and non-hallucinogenic 2a agonists, was unaffected. This model, and the parallel connection with dissociatives in the next section suggests both these agents may have a deeper common mode of action.

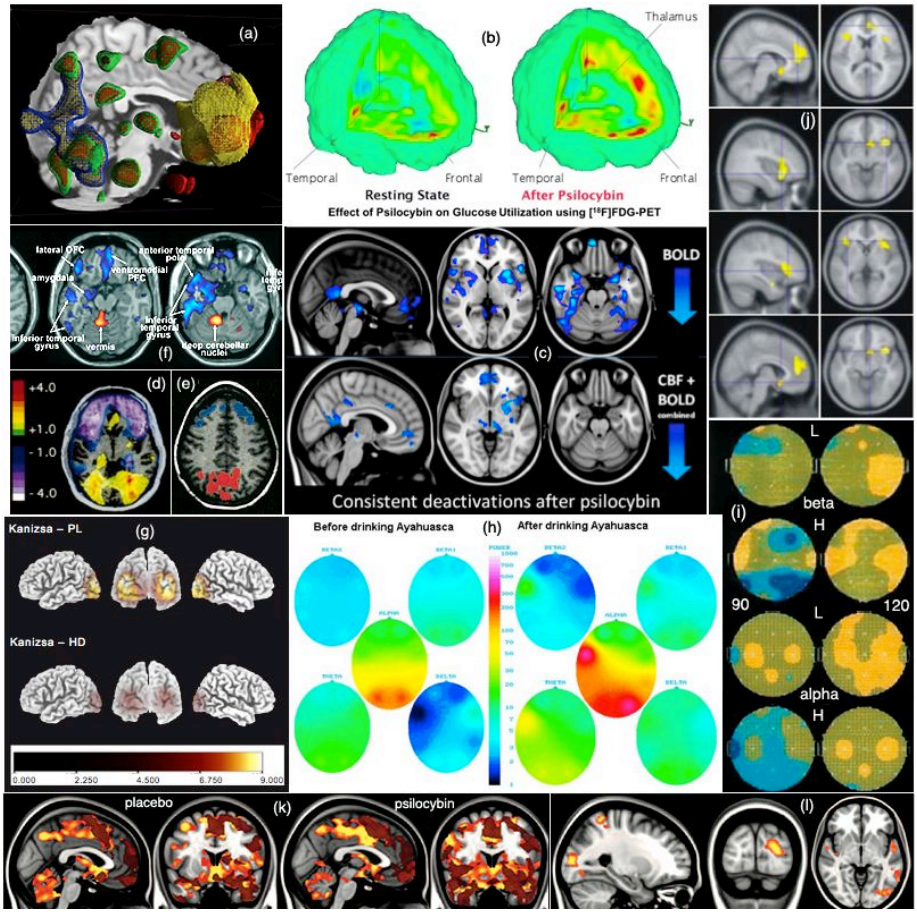


Fig 11: **(a)** PET study of 5HT2a sites where psilocybin acts with red and yellow having highest density (Hasler and Quednow). **(b)** PET study of 15-20 mg psilocybin taken orally over a 48 minute period 90 minutes after consumption, which shows frontal activation by comparison with a resting state (Vollenweider et al). This result contrasts markedly with a later fMRI study **(c)** of a recording during the 12 minutes after intravenous administration of 2mg (~15 mg orally), which shows reduced activity in medial frontal cortex (mPFC), posterior cingulate cortex (PCC) and other areas (Carhart-Harris et al 2012a, Lee & Roth). Franz Vollenweider, lead author of the first study commented: "We have completed a number of similar studies and we always saw an activation of these same areas. We gave the drug orally and waited an hour, but they administered it intravenously just before the scans, so one explanation is that the effects were not that strong." Neuropsychologist Keith Laws suggested confound anxiety at the stat of the experience: "Deactivation of the mPFC and PCC are linked to anxiety and anticipation of pleasant and unpleasant experiences. This is a stressful situation, even for experienced drug users, and I suspect that they measured something to do with anxiety" (Costandi, Laws, Zhao et al, Simpson et al). These results are compared with a PET **(d)** and fMRI BOLD study **(e)** of REM dreaming sleep compared with wakefulness, showing similar reductions in frontal activity and increases in occipital activity (Braun). Given the fact that subjects are still able to actively engage in trains of thought and conversation depending on the circumstances, both increases and decreases might be expected to be more extreme than the placebo state, depending on the degree to which the subjects are engaged in active ideation, as opposed to lying quietly in the apparatus as the effects just begin to come on. **(f)** PET scan of healthy women achieving clitoral orgasm shows similar frontal and other reductions with increases only in the deep cerebellar nuclei and vermis (Georgiadis et al, LePage). **(g)** Low resolution electromagnetic tomography sLORETA of subjects viewing a Kazaniga triangle showing disruption of their object-completion activation by psilocybin hallucinations (HD=high dose) (Kometer et al). **(h)** Activation of alpha, theta and delta EEG activity with reduced beta during an ayahuasca session (Hoffmann et al). **(i)** Reduced alpha and beta (and theta) in a second ayahuasca session, L, H doses at 90, 120 min (Riba et al 2002). **(j)** Increases in fMRI in frontal and paralimbic brain regions in an ayahuasca session (Riba et al 2006). **(k)** Increases in activity associated with autobiographical memories on psilocybin. **(l)** Greater late phase activations during autobiographical recollection under psilocybin than placebo (Carhart-Harris et al. 2012b).

Non-psychedelic serotonin modulators also have central roles as psychotropic drugs. MDMA, or 'ecstasy' has become famous as an entactogenic club drug. MDMA inhibits the vesicular monoamine transporter, which results in increased concentrations of serotonin, norepinephrine, and dopamine in the cytoplasm, and induces their release by reversing their respective transporters, resulting in a strong serotonin 'high' accompanied by oxytocin (Young) and dopamine release causing feelings of empathy and exhilaration. Most antidepressants enhance serotonin. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), both of which enhance serotonin levels are popular anti-depressants. Their effects may result partly from promoting neurogenesis in the hippocampus through secondary action on the glucocorticoid receptor (Anacker et al). Monoamine-oxidase inhibitor antidepressants also increase serotonin. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine and also acts on dopamine. Conversely, several atypical antipsychotics, are serotonin antagonists. Risperidone for example is believed to exert its effect through being a 5HT2a antagonist, but is also a broader-spectrum antagonist of serotonin, dopamine and nor-adrenaline.

Fig 11 gives an overview of a few studies looking at PET, fMRI and EEG in subjects under the influence of psychedelics. In the PET study subjects were given 15-20 mg of psilocybin by mouth and measured over a 48 minute period 90 minutes later. This shows an increase of frontal activity on psilocybin. Both ketamine and psilocybin led to a marked metabolic activation of the frontal cortex and a number of overlapping metabolic changes in other brain regions. Ego dissolution and derealization phenomena correlated with the increase of metabolic activity in the frontal cortex including the anterior cingulate, and also with changes in the temporal cortex and basal ganglia (Vollenweider et al 1997a). Vollenweider considers this to support the CSTC model. In a comparable study on ayahuasca increased blood perfusion was observed bilaterally in the anterior insula, with greater intensity in the right, and in the anterior cingulate/frontomedial cortex of the right hemisphere, implicated in somatic awareness, subjective feeling states, and emotional arousal. Additional increases were observed in the left amygdala/parahippocampal gyrus, a structure also involved in emotional arousal (Riba et al 2006).

By contrast, the second fMRI study (Carhart-Harris et al. 2012a) taken for just 12 minutes after a much smaller 2 mg intravenous injection of psilocybin scaled to approximate the intensity of a larger oral dose. Here the subjects had barely had time to adjust to their experience and were measured only for a few minutes, so as noted above, the scan may have measured anxious anticipation as the effects became pronounced rather than the activity of a person accustomed to the effects of their experience. It has been associated with a reduction in activity of the default network. A drop in prefrontal activation would be consistent with an experience of watching the process without attempting to exert control over it, as noted previously in the glossolalia study and in dreaming REM sleep, as illustrated above. This study has an eerie similarity to the effects of female orgasm, satirically described as a 'complete turn off'.

In a subsequent experiment (Carhart-Harris et al. 2012b) to test whether psilocybin facilitates access to personal memories and emotions comparing responses to autobiographical memories under psilocybin and placebo, robust activations to the memories were seen in limbic and striatal regions in the early phase and the medial prefrontal cortex in the late phase in both conditions. There were additional visual and other sensory cortical activations in the late phase under psilocybin that were absent under placebo. Ratings of memory vividness and visual imagery were significantly higher after psilocybin and there was a significant positive correlation between vividness and subjective well-being at follow-up.

The field remains sparse due to the effective suppression of virtually all human scientific research over half a century, stemming from their schedule 1 classification. There are other substantial problems due to the variable nature of the setting route of administration, whether they are meditating, or thoughtlessly watching the patterns or the novel appearances, or their mind is racing while suffering a bout of anxiety, and whether the subjects are engaged in an active task, which they may or may not relate to under the influence, or actively enjoying the experience and its effects. Given the fact that psychedelics are agents that can have profound affects on what we are engaging with, but which enable people to engage in a variety of activities, enhancement or reduction of brain activity in given regions will be highly variable.

Four EEG studies likewise show up the difficulties of setting a meaningful experimental paradigm. The first looks at low-resolution electromagnetic tomography of a person looking at a Kazaniga triangle showing the activation associated with object completion is diminished. The experimenters correctly conclude that the subjects 'hallucinations' may be masking the basic task processing. The second two show that subjects on ayahuasca have some general reductions in the EEG power of their alpha, beta and theta waves, which again is to be expected just from mood changes and the fact that they are dealing with a mind-altering

experience. A fourth study (Stuckey et al) of two experienced ayahuasca users clarifies these results, showing increases in global EEG coherence in the gamma band believed to accompany perceptual and cognitive processes (36-44 Hz and 50-64 Hz) along with increased modal EEG alpha frequency and global power decreases across the cortex in most frequency bands, suggesting increased gamma processing reducing power in other modes, consistent with the Zen EEG results.

In a behavioral study (Kometer et al 2012), psilocybin enhanced positive mood and attenuated recognition of negative facial expression, increased goal-directed behavior toward positive compared with negative cues, facilitated positive but inhibited negative sequential emotional effects, and attenuated the P300 event related potential. In a long term study on traditional peyote use the peyote group showed no significant deficits compared those with minimal substance use, on the Rand Mental Health Inventory or any neuropsychological measures, whereas a former alcoholic group showed significant deficits on every scale of the RMHI and on two neuropsychological measures. Within the peyote group, total lifetime peyote use was not significantly associated with neuropsychological performance (Halpern et al. 2005).

Nevertheless two things are clear. Firstly although psychedelics do cause profound changes to the subjects sensory processing so they see patterns, hear sounds, experience synaesthesias and may experience complex visions, all of these require the same sorts of complex brain processing we know take place in waking life and in dreaming REM sleep. Secondly, unlike the scopolamine of datura and related species, where people can no longer distinguish between the things they are seeing and the world around them, people on psychedelics know they are perceiving additional sensory experience, but they generally have no trouble distinguishing this from external reality, except perhaps for short periods after entering a deep repose, or when their thoughts are transiently disrupted. Thus, although there may be some elements of distortion of time and space processing (Wittmann et al), underlying brain functions remain intact. We thus cannot expect gross disabling changes in cortical processing, and should find variability depending on the set and activity or otherwise taking place.

Furthermore we need to understand that changes in serotonin receptors have slowly varying long-term effects not consistent with the vast dynamic changes psychedelics impose on consciousness. In fact the binding of an agonist such as psilocybin has a half-life of receptor activation of some hours, so we need to look deeper into the more rapidly changing aspects of brain dynamics, such as the changes in pyramidal glutamate-based excitation, to gain an insight into how these changes in consciousness occur.

We thus turn to another intriguing possible connection between serotonin receptor psychedelics and the equally bizarre subjective affects of NMDA antagonist dissociatives such as ketamine and PCP, which may have a deep commonality of action through their related actions on glutamate activation through similar reciprocally opposite interactions of NMDA blocking agents with mGluR2. This suggests these two very different classes of agent may give rise to common deep similarities of visionary effect, as noted in the subjective case study at the end of this paper.

There are three neurotransmitter models of psychosis. The first involves the dopamine D2 receptor, exemplified by the paranoid psychosis accompanying methamphetamine overdose, and antagonized by the typical antipsychotics The second, that of atypical anti-psychotics involves 5HT2a antagonists. Thirdly we have those involving glutamate mGluR2 agonists. Thus we are discovering that several of the pieces of the psychedelic puzzle appear to be coming together into a common explanation of psychosis as well (Snyder, González-Maeso et al. 2008, Moreno et al 2011b). However the notion that psychedelics are psychotomimetic, or form a model for schizophrenia, is a dangerous and confused generalization, contradicted by the capacity of psychedelics to induce long-term positive life-changing experiences in controlled studies (Griffiths et al, Barbosa et al).

Fig 12 illustrates the putative mechanism by which the action of the psychedelics and dissociatives might each have linked dynamics through a common opposing action with mGluR2. Features of this mechanism remain to be replicated although the work by Gonzalez-Maeso's group has been well documented. The actual sites of differential activations of all three receptors 5HT2a, mGluR2 and NMDA, whether in the prefrontal or other cortices, thalamic or other sub-cortical centres, whether they are pre- or post-synaptic, and whether they are merely cross-talk or arise from hetero-duplexes all remain uncertain, although the expression of *egr*-2, fig 10, suggests the 5HT2a psychedelic action is cortical. Nevertheless this receptor relationship does open an intriguing basis for a common action of both visionary and anti-psychotic changes to the central nervous system. Moreover, on the basis that mGluR2 agonism reduces overall glutamate excitability through inhibiting the c-AMP chain, this provides a possible central mechanism for

entheogens catalysing rapidly changing phenomena in conscious experience through the smoothing effects of mGLUR2 glutamate inhibition being reduced via serotonin agonism linked to suppression of mGluR2. Findings also suggest that the glutamatergic surge mediated by 5HT2a receptors in cortical neurons leads to increased expression of AMPA receptors causing the release of brain derived neurotrophic factor (BDNF), suggesting that psychedelics contribute to enhanced neural plasticity (http://neurowiki2012.wikispaces.com/Entheogens+and+the+Brain).

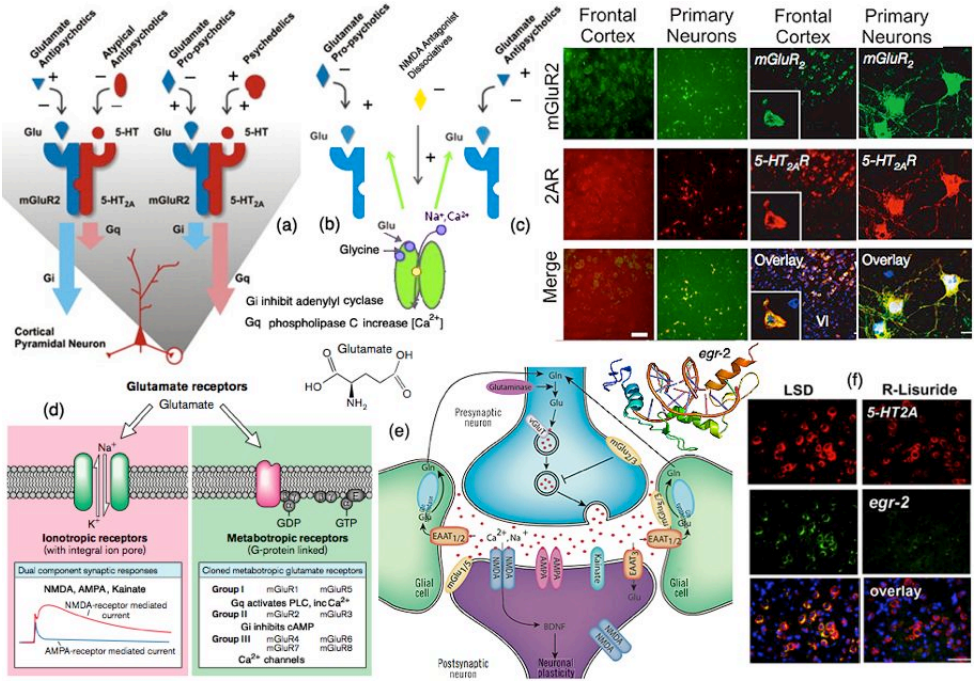


Fig 12: (a) Hypothetical push-pull heteroduplex formation between mGluR2 and 5HT2a and its opposing effects on psychedelics and anti-psychotics (Fribourg et al). This heteroduplex action has not been fully replicated in a related study although cross-talk has been established (Delille et al). Upper row + agonist, - antagonist, lower row + psychedelic/pro-psychotic. - anti-psychotic. (b) Parallel opposing mechanism between NMDA dissociative antagonists and mGluR2 (Dong et al, Moghaddam & Adams), which may arise from subcortical NMDA inhibition of prefrontal pyramidal glutamate release (Lorain et al, González-Maeso & Sealfon, Gonzalez-Maeso et al 2007, 2008) but since group II mGluR agonists have also been found to enhance NMDA currents (Tyszkiewicz et al) the two may act on the same synaptic junctions. This process appears to work through PKC phosphorylating NMDA directly through a phospholipase C and inosine-triphosphate pathway. Conversely studies using in vivo microdialysis have confirmed that administration of NMDA channel blockers causes increased glutamate release in frontal cortex (Delille et al). AMPA glutamate antagonists are also able to antagonize hyperactivity induced by PCP NMDA blockade in rats. NMDA antagonists have also been found to interact with 5HT2a sites extending the relationship (Martin et al, Millan et al). (c) Staining correspondence between 5HT2a and mGluR2 shows corresponding cellular locations apparently to the dendritic and synaptic level (Fribourg et al, Gonzalez-Maeso et al 2008). (d) Glutamate receptor types (ex Forsythe & Barnes-Davies). (e) Involvement of glutamate receptors at the synaptic junction involves a variety of mGlu G-protein linked types, pre- and post-synaptically and on glial astrocytes (Loane et al), as well as NMDA and AMPA and Kainate ionotropic channels (Kelmendi et al). Although mGluR2 occurs presynaptically to modulate glutamate release it also does occur post-synaptically (Petralia et al, Renger et al, Tyszkiewicz et al). (f) Corresponding images for LSD and R-lisuride showing differing *egr*-2 expression (Gonzalez-Maeso et al 2007). *Egr*-2, also called Krox-20, is associated with early development of the CNS, and is widely expressed in the CNS, in neuronal conduction and repair (Mengozzi et al), neuronal plasticity and long-term potentiation in memory. Paradoxically although psychedelics result in *egr*-2 expression, NMDA blockers, inhibit *egr*-2 expression in the hippocapus (Williams et al), however psychedelics do not appear to express *egr*-2 in the hippocampus either (fig 10). Changes in its expression are also associated with autism (Swanberg et al).

5: Doors of Dissociation: Ketamine and the NMDA Receptor Antagonists

Dissociative hallucinogens, such as ketamine (Jansen), are antagonist blocking agents of the NMDA or n-methyl-d-aspartate ionotropic receptor, which promotes activation, learning and memory processes. Dissociatives are a class of hallucinogen anesthetics, which reduce or prevent signals from various parts of the brain reaching the conscious mind. The NMDA receptor's connection with the memory formation process and the fact that they act in the hippocampal formation and prefrontal cortex, explain ketamine's profound effects on memory and thought. As noted in fig 12, cortical effects of dissociatives may result from subcortical NMDA blockage. These effects inhibit the filtering function of the brain and may mirror the sensory overload associated with schizophrenia and may include experiences of flying and union with god. Ketamine is also a weak μ-opioid agonist (Sarton et al).

At sub-anesthetic doses, they alter many of the same cognitive and perceptual processes affected by other hallucinogenic drugs such as mescaline, LSD, and psilocybin; hence they are also considered hallucinogenic, and psychedelic with additional dissociative effects, including: depersonalization, the feeling of being unreal, disconnected from one's self, or unable to control one's actions; and derealization, the feeling that the outside world is unreal or that one is dreaming. At sufficiently high doses, users may experience what is coined the "K-hole", a state of deep dissociation whose effects are thought to mimic the phenomenology of schizophrenia (Giannini, Deakin et al) and near death experiences (Jansen).

Timothy Leary observed that ketamine and Salvinorin A were the most profound psychedelic drugs in terms of the perceived depths of the experience (Leary & Sirius).

Although the direct action of the dissociatives is through a completely different pathway from psychedelics, it may have a common basis of action, through interactions with the mGluR2 G-linked glutamate receptor, which from the previous section, is linked in turn with the 5HT2a serotonin receptor of psychedelics, as already detailed in fig 12. Potentiation of the glutamate receptor mGluR2 by biphenyl indanone-A (BINA) inhibits the effects of NMDA dissociatives in animal studies - phencyclidine (PCP)-induced hyperlocomotion and prepulse inhibition deficits in mice (Hackler et al). The mGluR2 agonist LY379268 likewise ameliorates the effects of NMDA antagonist MK-801, (ibid, Dong et al), suggesting dissociatives such as PCP and ketamine, may have an indirectly common pathway of psychedelic action. Research has also shown that mGluR2 agonists reversibly increase NMDA receptor currents and antagonists reduce them, providing a similar link between NMDA and mGluR2 (Tyszkiewicz et al, Kammermeier).

The electroencephalographic and PET and fMRI scan results for ketamine are somewhat contradictory just as they were for psilocybin (Vollenweider et al 1997d, Deakin et al, Holcomb et al). Some PET studies show prefrontal activation on ketamine while others show consistent deactivation. One EEG study has seen an increase in gamma activity, suggesting increased processing (Maksimow et al). Mismatch negativity, a preattentive auditory event-related potential generated by a stimulus that deviates e.g. in pitch, intensity, or duration, from a repeated series is an NMDA related function, which predicts the strength of ketamine but not psilocybin effects in a given individual (Umbricht et al).

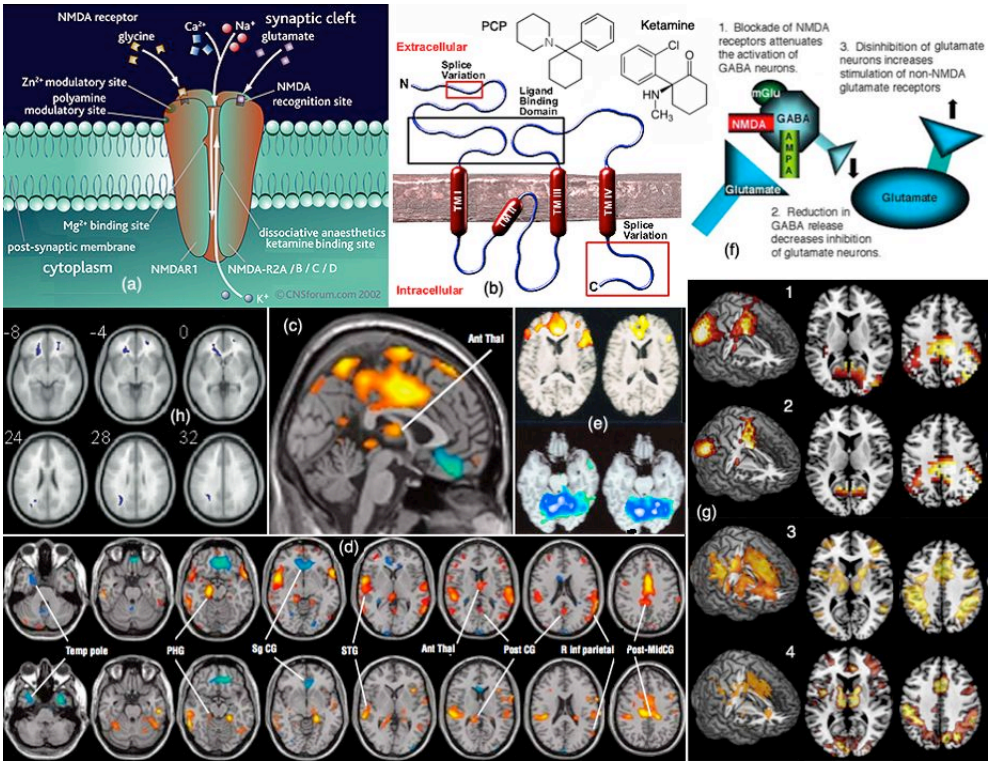


Fig 13: (a) Structure of the NMDA ionopore receptor, (b) protein structure with splice variations. The receptor is activated by glycine together with glutamate, with the ketamine-blocking site mid channel (CNSforum.com). (c) Effects of ketamine using fMRI BOLD. Warm colours increases in activity, cool decreases (Deakin et al). Ketamine induced a decrease in ventromedial frontal cortex, including orbitofrontal cortex and subgenual cingulate, consistent with its dissociative effects, and increased activity in mid-posterior cingulate, thalamus, and temporal cortical regions. (d) Inhibition of ketamine activity by lamotrigine, a sodium channel blocker that decreases glutamate release (Deakin et al). (e) PET increases (frontal and anterior cingulate) and decreases (cerebellum) on administration of ketamine (Holcomb et al). (f) Proposed mechanism to explain pyramidal cell excitation through NMDA inhibition of GABA neurons (Krystal et al 2003). (g) sLORETA (EEG) attenuation of P300 response to oddball visual task 1 placebo 2 ketamine, fMRI BOLD reduction 3 placebo, 4 ketamine (Musso et al). (h) White matter decrements in long-term ketamine users (Liao et al).

The effects of ketamine and NMDA blocking antagonists on glutamate driven excitation may be dosage dependent, with smaller sub-anaesthetic doses causing excitation while larger doses cause a reduction. A suggested mechanism for the excitation at lower doses is NMDA antagonism suppressing GABA inhibition of pyramidal excitation. This phenomemon in rodent studies led to concern at the description of Olney's 'holes in the brain' lesions in rodents (Olney et al 1989). Olney and Farber (1995) suggested that NMDA antagonists block excitation of gamma-aminobutyric acid (GABA) interneurons, resulting in removal of GABA restraint of cholinergic, serotonergic, and glutamatergic afferents to posterior cingulate cortex. This, they suggested, caused a triple excitotoxic effect on posterior cingulate pyramidal cells, accounting for the focal neurodegeneration they had observed after phencyclidine administration. However Olney's lesions in rodents have not been replicated in primates, possibly because of species differences in neuroexcitation.

In addition to its anesthetic and hallucinogenic effects, Ketamine has been found to be a potent anti-depressant (Berman et al, Correll & Futter, Maeng & Zarate, Zarate et al). It has also been shown to provide antidepressant affect for a week after a single dose, acting in part by increasing synthesis of BDNF, a nerve growth factor that supports the health of brain cells, helps them grow and can promote the development of new neurons. (Autry, Szalavitz 2011b). It has also been suggested that the resulting glutamate activity may induce synaptogenic changes helping the depressed brain repair itself (Murphy). This action is potentiated by a single dose of GSK-3 inhibitors such as lithium chloride (Liu et al).

That said, many recreational users of ketamine report signs of negative effects from long-term recreational use, including memory deficits (Morgan et al, Curran & Morgan, Morgan & Curran), sleep paralysis, semi-permanent visual changes, long term tolerance which may be associated with changes in the numbers of their NMDA receptors or the elicited protein profiles, and white matter decrements. Notable proponent John Lilly was for years in and out of hospital due to ketamine bouts and Marcia Moore died apparently having injected herself with ketamine, entering a hypothermic coma in a wintery forest (Jansen). My own experience of ketamine is included in the case study.

6: Salvinorin-A and κ-Opioid Dissociatives

The diterpenoid κ-opioid agonist Salvinorin A is the main active psychotropic molecule in Salvia divinorum, a Mexican plant which has a long history of use as an entheogen by indigenous Mazatec shamans. Salvinorin A is considered to be a dissociative, exhibiting atypical psychedelic effects, including sensations of motion, or being pulled or twisted by forces, visions of membranes, films and various two-dimensional surfaces, merging with or becoming objects, overlapping realities, such as the perception of being in several locations at once, uncontrollable laughter, past memories, such as revisiting places from childhood memory and strange memories that things have always been this way (Turner).

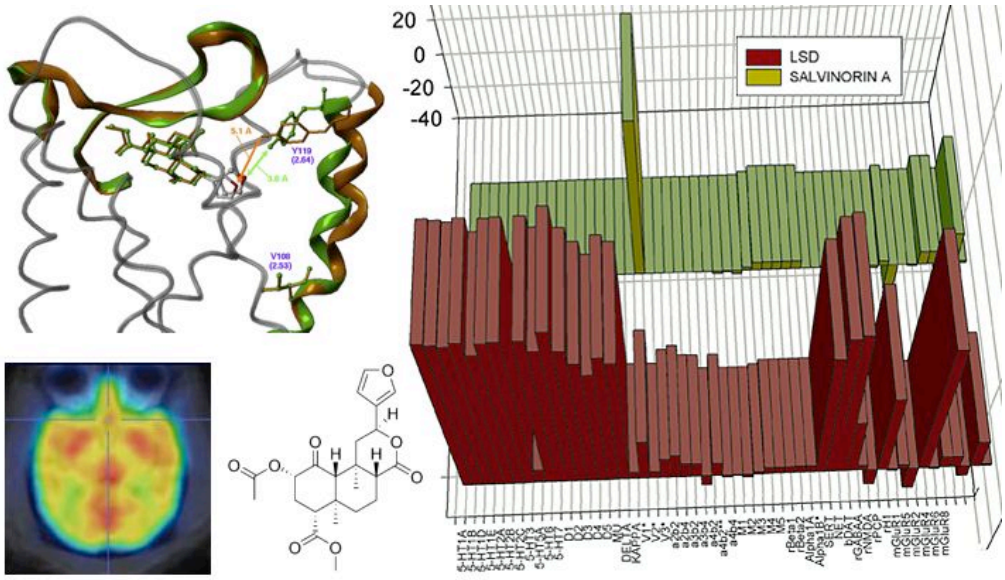


Fig 14: (Left) κ-opioid receptor with salvinorin-A attached (Vortherms et al) with below a baboon PET scan showing [^{11}C]-salvinorin A binding 3-7 mins (Hooker et al) and the salvinorin-A diterpinoid molecule. Onset of binding was extremely rapid and faded after 7 mins. (Right) Salvinorin-A and LSD receptor binding profiles compared showing kappa selectivity for salvinorin and broad spectrum affinity for LSD across 5HT and dopamine receptors with a notable negative interaction with mGluR2 and rNMDA (Roth et al).

There are three classes of opioid receptor, μ, δ, and κ. While the former two cause dependence and manifest co-dependence, which may result from their enhancement of the mesolimbic dopamine system,

κ-opioid receptor KOPr agonists produce an aversive effect. The κ-opioid receptor and its endogenous ligand dynorphin are enriched in the ventral tegmental area, involved in dopamine release and the nucleus accumbens and prefrontal cortex regulating mood and motivation. κ-opioid receptor activation in these regions decreases dopamine transmission, explaining the dysphoric reaction (Shippenberg). There is also evidence κ-opioid receptor agonists can alleviate the symptoms of opiate withdrawal. Opiates are agonists for the μ-opioid receptor and because κ has an opposing action to μ it appears to be able to redress the opioid receptor balance sufficiently to facilitate withdrawal (Pfeiffer et al).

This is the basis of the use of ibogaine in addiction treatment (Ross). Because of the ibogaine molecule's tryptamine core, it acts as an agonist for the 5-HT2a receptor set like other psychedelic tryptamines (such as DMT and psilocybin) and other serotonergic psychedelics like LSD and mescaline. However what makes ibogaine's pharmacodynamic properties and subjective experience unique from that of other psychedelic tryptamines and serotonergic psychedelics is that it also acts as a dissociative through antagonism of the NMDA receptor set (like ketamine) as well as acting as an agonist for the κ-opioid receptor (like salvinorin A). Ibogaine's agonism of the κ-opioid receptors is thought to be what is responsible for its anti-addictive properties, as salvinorin A exhibits a similar alleviation of withdrawal symptoms in individuals addicted to opiates and methamphetamine. However ibogaine also has an α3β4 nicotinic antagonist effect, a mechanism of action shared with anti-smoking drugs like bupropion and mecamylamine, as well as methadone, which may also be responsible for its effects on addiction.

Both κ-opioid agonists and NMDA antagonists are classed as dissociatives and have subjective effects with remarkably significant parallels, suggesting there is also a commonality of action between these two as well. The research here is sparse, but there are some indications of a functional connection (Sershen et al, Trujillo) and the action of ibogaine on opiate addiction has been attributed to a combined effect of its NMDA antagonist and κ-opioid agonist properties (Glick et al).

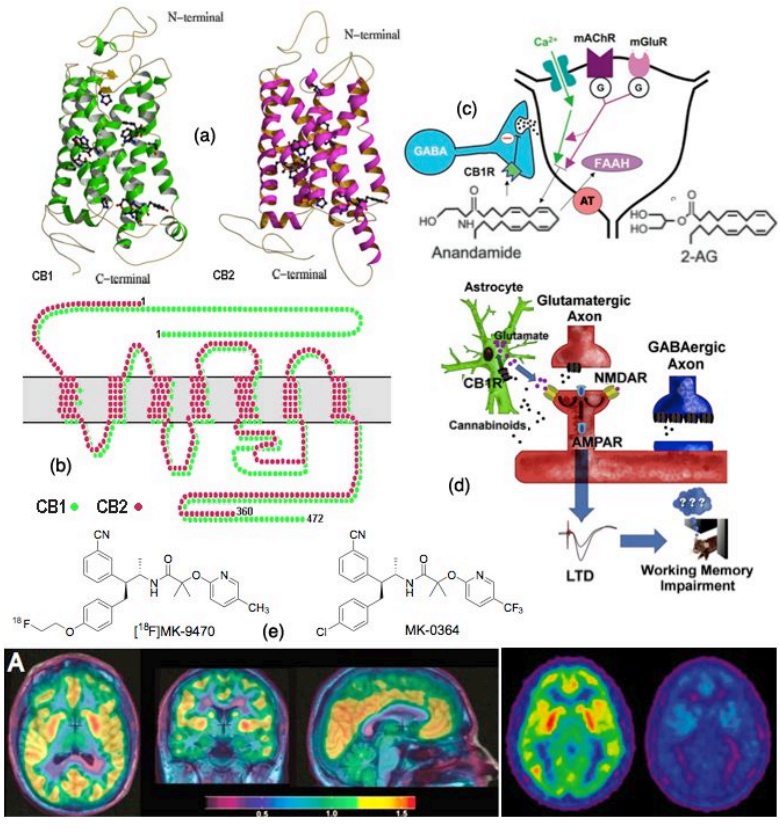


Fig 15: (a) Structures of the central nervous cannabinoid CB1 and immune system CB2 receptors (Montero et al) (b) 2-D representation in the membrane (Wikipedia) (c) Action of natural cannabinoids on GABA neurons coupled to pyramidal neurons (Alger) (d) Interference with working memory is believed to result from secondary action of glial astrocytes on hippocampal pyramidal, cells resulting in long term depression (Han et al) although the direct action of cannabinoids on these cells is excitatory (Kawamura et al). Opiates also show glial-linked effects (Bland et al.) (e) PET mapping of CB1 receptors in the brain using the cannabinoid agonist [^{18}F]MK-9470, with confirmatory displacement by the competitive antagonist MK-0364 at right (Burns et al).

7: Cannabinoids

Although they are not psychedelics, cannabinoids have to be classed as entheogens, because cannabis has been used for centuries, as a spiritually transformative agent, from the Shiva sadhus of India through the San Bushmen of the Kalahari to the Rastafarians.

Cannabinoid receptors have a variety of functions. CB1 occurs widely in the brain and CB2 is expressed on cells of the immune system where it has an immunomodulatory effect, reducing inflammatory response where it plays a role in processes including implantation of the fertilized embryo. Debate about the significance of the effects of cannabis and its principal active cannabinoid (-)-trans-Δ9-

tetrahydrolcannabinol, or THC, on the capacity of the immune system to target infectious disease and cancer continue with conflicts between laboratory studies (Klein et al, Hegde et al, Gabrilovich & Nagaraj, Pacifici et al, Roth et al, Zurier) and social heath statistics on HIV patients using medicinal cannabis, which see no deleterious effect (Kaslow et al).

The active endogenous ligands for CB1 and CB2 are anandamide (Devane et al) and 2-AG, or 2-arachidonylglycerol, (Pertwee) both of which are close derivatives of arachidonic acid, a principal fatty acid which is a second signalling molecule involved in the cleavages of phospholipases C and A2 in the 5HT2 receptor, and a component of key phospholipids such as phsophatidyl-choline and is one of the most abundant fatty acids in the brain. A psychoactive andamide transporter FLAT has been discovered (Fu et al, Marsicano & Chaouloff).

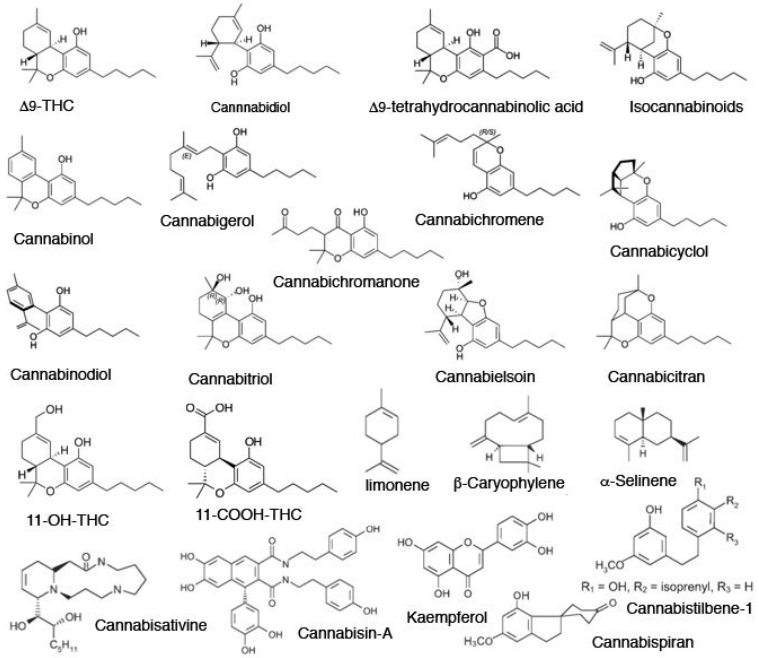


Fig 16: Natural cannabis molecules show a great deal of diversity. While THC is the principle psychoactive, cannabidiol has anti-psychotic properties. Action in the immune system CB2 receptors modulates immunity and reduces inflammation. There are also significant angiogenesis inhibiting and anti-oxidant components.

CB1 receptors are thought to be one of the most widely expressed G protein-coupled receptors in the brain. This is due to endocannabinoid-mediated depolarization-induced suppression of inhibition, a very common form of short-term plasticity in which the depolarization of a single neuron induces a reduction in GABA-mediated neurotransmission. CB1 knockout mice do respond to THC, which shows that either CB2 or unknown cannabinoid receptors also have pharmacologic significance (Zimmer et al). However mice lacking glial receptors have no memory deficit although those lacking neuronal receptors do, showing glial activation is responsible for the memory effects of cannabinoids (Williams R).

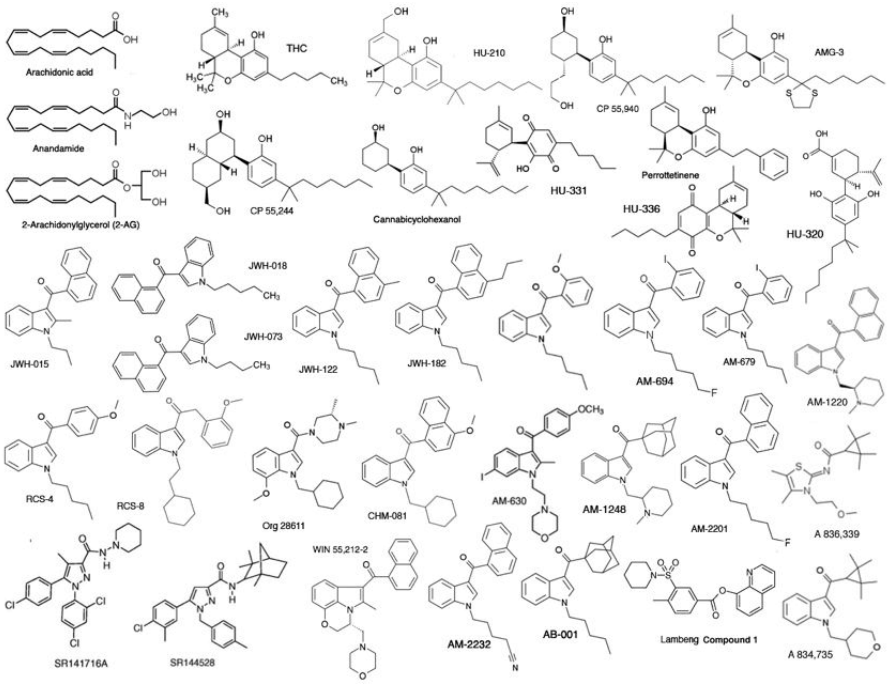


Fig 17: Natural and synthetic cannabinoids grouped by type. Top-left natural active cannabinoids anandamide and 2-AG are minor modifications of the major brain fatty acid arachidonic acid. Successive modifications to the right produce super-potent variants of THC. Other variants such as the JWH series are based on the naphthoyl-indole (Huffman et al) and arylsulfonamide structures (Lambeng). Three synthetics related to cannabidiol are HU-320, which has strong antiinflammatory and immunosuppressive effects but no psychotrophic effect, HU-331 with efficacy against oncogenic human cells, by strongly inhibiting DNA topoisomerase II with negligible effect on topoisomerase I, and HU-336 a strong angiogenesis inhibitor. Perrottetinene is a natural putative cannabinoid found in *Radula marginata*.

Brain regions in which cannabinoid receptors are very abundant are the basal ganglia, associated with movement control; the cerebellum, associated with body movement coordination; the hippocampus, associated with learning, memory, and stress control; the cerebral cortex, associated with higher cognitive functions; and the nucleus accumbens, regarded as the reward center of the brain.

They are also associated with fear extinction in situations of risk of injury. The endocannabinoids anandamide and 2-arachidonoylglycerol are degraded by fatty acid amide hydrolase (FAAH). The FAAH inhibitor, AM3506 (5-(4-hydroxyphenyl)pentanesulfonyl fluoride) decreased fear during a retrieval test in a mouse model of impaired extinction. Mice carrying a low-expressing FAAH variant exhibited quicker habituation of amygdala reactivity to threat, and had lower scores on the personality trait of stress-reactivity (Gunduz-Cinar O et al).

Δ9-THC is only one of a very diverse series of bioactive molecules present in the cannabis plant, a sample of which are illustrated in fig 16. Several others have differing action, either as antioxidants, or possible angiogenesis inhibitors. Cannabidiol has been found to have anti-psychotic properties (Leweke et al, Zuardi et al), which may offset some of the negative side effects of paranoia that can accompany some cultivated high-THC forms of cannabis extract. However the sheer variety of these compounds makes cannabis an effective phytochemical shotgun. Nevertheless millennia of cultural use suggest its use as a medicinal and recreational substance is not profoundly harmful. There has never been a documented human fatality from overdosing on tetrahydrocannabinol or cannabis in its natural form.
Certain tumors, especially gliomas, express CB2 receptors. Δ9-THC and WIN-55,212-2, two non-selective cannabinoid agonists, induce the regression or eradication of malignant brain tumors in rats and mice (Galve-Roperh et al). CB2 selective agonists are effective in the treatment of pain, various inflammatory diseases in different animal models, osteoporosis, atherosclerosis and Alzheimer's (Ofek et al, Steffens et al. Whiteside et al). Brain scans show the affect on pain is by reducing its emotional impact (Lee).

The fact that active cannabinoids are modified fatty acids means that a wide spectrum of molecules with significant hydrophobic character and appropriate hydrogen bonding in their folded state can act with varying affinities as CB1 and CB2 agonists. Fig 17 shows a variety of these, including modifications of THC with increased potency. For example HU-210, HU for Hebrew University, (Mechoulam et al) has 100-800 times the potency of THC which itself is active in quantities of around 1-5 mg. It also encourages hippocampal neurogenesis and thus has anti-anxiety and antidepressant effects (Jiang et al). It is also implicated in preventing inflammation caused by amyloid beta proteins in Alzheimer's disease, in addition to preventing cognitive impairment and loss of neuronal markers, induced through the activation of cannabinoid receptors, which prevents microglial activation that elicits the inflammation (Ramírez et al).

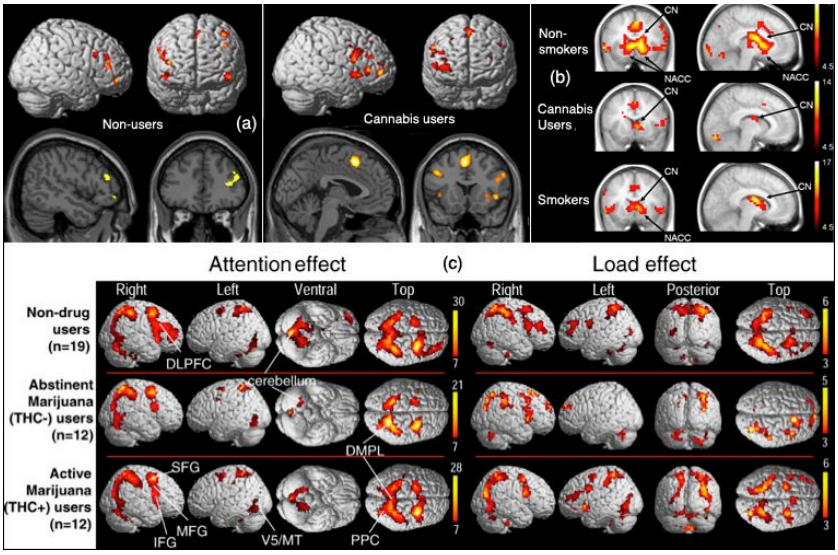


Fig 18: (a) Recent cannabis users displayed greater and more widespread brain activation than normal subjects when attempting to perform a spatial working memory task. This observation suggests that recent cannabis users may experience subtle neurophysiological deficits, and that they compensate for these deficits by "working harder" - calling upon additional brain regions to meet the demands of the task. Short-delay response task minus a perception task control (Kanayama et al). (b) Reward anticipation activity in the caudate nucleus is lowered in cannabis users (van Hell et al), (c) Evidence of reorganized visual-attention network and cerebellar hypoactivation. Subjects are instructed to track 2, 3 or 4 of 10 moving balls on a screen once the target balls are identified (4 are highlighted in the figure), and push a response button if the same target balls are re-highlighted. Surface maps demonstrate the effect of attention (independent of load, left) and the effect of attentional load (increasing difficulty from tracking 2 to 3 to 4 balls, right) cannabis users had different brain organization although there were no significant differences in performance on this task, nor in all but 2 of 31 other neuropsychological tests (Chang et al 2006).

The JWH family named after John W. Huffman, of Clemson University, consists of naphthoylindoles (Huffman et al). JWH-018 is a full agonist of both the CB1 and CB2 cannabinoid receptors and has been associated with unpleasant effects, including seizures, possibly associated with GABA inhibition and dissociative and anxiety episodes. There have been few studies of the metabolites of synthetic cannabinoids (Zhang et al, Kraemer et al) suggesting some reactive epoxide metabolites.

This paucity of real information comes amid conflicting unsubstantiated accounts of cancer in mice (Morris), and anonymous reports linked to suppliers showing no deleterious effects (Synchronium). JWH-073 acts as a partial agonist at both the CB1 and CB2 cannabinoid receptors. It is five times more selective for the CB2 subtype. JWH-081 by contrast is ten times more selective for CB1. Other cannabinoid types include the diverse AM-series named after Alexandros Makriyannis of Northeastern University and the arylsulfonamide type (Lambeng et al). Two fluorinated compounds XLR-11 and AM-2201 have recently been associated with acute kidney damage (Murphy et al).

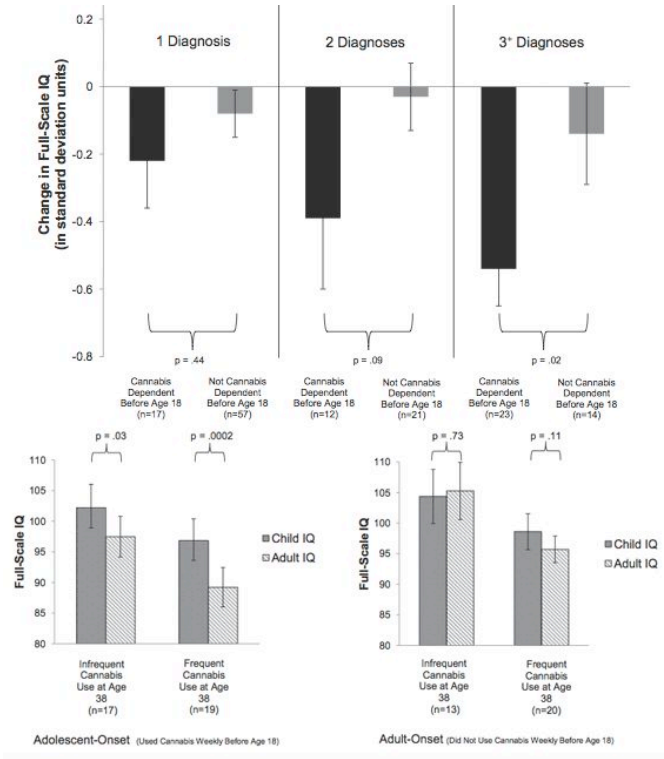


Fig 19: Significant decline in adult IQ associated with cannabis use in adolescence before the brain has fully developed (Meier et al).

The sheer diversity of these cannabinoids, combined with the obvious capacity to design further and further analogues shows that the war on drugs, as applied to cannabinoids, is both damaging and futile. Given potent synthetic cannabinoids with either CB1 or CB2 selectivity, one can separate agents acting primarily on the brain from those acting on the immune and other peripheral systems (Gardin et al). Sequential banning of every molecule which appears as a legal alternative to cannabis, or alrady banned cannabinoids, simply knocks out the best molecules discovered, resulting in an ad-hoc mix of any molecule someone can come up with a novel design for, which doesn't mimic known banned configurations, but still acts on the cannabinoid CB1 receptor, whose side effects are not yet known. Either one has to declare any change to brain receptors illegal, which is impossible, since our endogenous neurotransmitters and many therapeutic drugs do precisely this, or legitimize cannabinoids that have good selectivity and minimal side effects.

While cannabis has been used for millennia as an intoxicant, there is evidence for a variety of potential long-terms effects on the brain, immune system and hormonal systems. The effects on the immune system are immunomodulatory, and may reduce inflammatory (Zurier R et al) and auto-immune conditions, but do appear to result in a reduction of killer cells (Klein et al, Pacifici et al) and massive mobilization of myeloid-derived suppressor cells with potent immunosuppressive properties (Hegde et al). Animal models show that cannabinoids alter multiple hormonal systems, including suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and the activation of hypothalamic, pituitary and adrenal systems, by binding to the cannabinoid receptors in the hypothalamus. Despite this, the effects in humans have been inconsistent. The long-term consequences of marijuana use in humans on endocrine systems remain unclear (Brown & Dobs). In a 2012 genetic study (Lachance et al) it was found the the Hadza gatherer-hunters of Tanzania have evolved a novel CB2 receptor gene suggesting adaption to immune responses to disease resulting from their traditional cannabis use.

Long-term effects on the brain remain ambiguous. A 2012 study (Meier et al) has shown that use of cannabis in adolescence (before 18) has a marked detriment of up to 8 points in subsequent adult IQ scores, demonstrating that cannabis should not be taken by adolescents, but the effects when use begins in adulthood, even resulting in dependence are marginal. A followup study, which takes into account social status factors as confounds has contradicted these findings (Garrett-Walker 2013). In a study of long-term marijuana users (Jager et al) fig 20(e) no firm evidence was found for long-term deficits in working memory

and attention. However there were subtle dynamic differences in processing. In the superior parietal cortex, cannabis users failed to reduce activity in response to practice, compared with controls. In (para)hippocampal regions and the right dorsolateral prefrontal cortex there was reduced activity, however, lower brain activation was not correlated with changes in tissue composition and was unrelated to associative memory performance. Similar results have been found in the three studies discussed in detail in fig 18. For a current review of acute and long-term studies see Bhattacharyya & Sendt (2012).

Cannabis has been ambiguously associated with schizophrenia, but the evidence is inconclusive and it is possible the association is because schizophrenics find it alleviates their symptoms (Szalavitz 2010). Two studies have suggested a possible causal link (Arseneault et al, Andréasson et al) however there is no evidence for increasing rates of schizophrenia in countries with massive increases in cannabis consumption nor lower rates in countries with low consumption (Degenhardt L, et al, Frisher et al). One possible source of concern is young people carrying two copies of the short version of the COMT (catechol-o-methyl transferase) gene, which breaks down dopamine. A research study in NZ shows this group to be 10 times more likely to develop psychosis, smoking cannabis as a teenager (Lawton 2005).

8: Ecstasy and the Entactogens

The entactogens have been included within the entheogen orbit because their emotional effects have made them the key to modern forms of ritual psychotropic agent use, associated with positive celebration of interconnectedness. Ecstasy, or MDMA, is the clear favourite among a series of mood enhancing molecules that work as serotonin releasing agents, promoting empathy and human bonding as well as acting as stimulants and sensory enhancers, leading to world-wide popularity. Its metabolite MDA has also been used as an entactogen psychedelic and some phenylethylamine psychedelics such as 2C-B are also regarded as entactogens. However attempts to make non-toxic variants such as MDAI (Nichols et al 1990) are less regarded for the quality of their effect and have been banned despite their lack of toxic effects. My own experience of MDMA is included in the case study.

The story of Ecstasy's action and the possible routes of any long-term damage are as complicated and challenging as the mechanisms of psychedelic entheogens. As already noted in fig 5, initial reports of serious neurotoxicity and blanket depletion of serotonin system function (McCann et al), disruption of serotonin axonal pathways (Hatzidimitriou et al), and dopamine damage, even on a single dose (Ricaurte et al), have proven to be bad science, with a key research paper retracted (Holden). Initial reports of Ecstasy causing Parkonsinism through dopamine damage also appear to be unfounded (Jerome et al) with later reports suggesting MDMA is protective against existing Parkinsons symptoms (Concar). Ecstasy has also been found to be of long-term benefit in therapy for trauma and post-traumatic stress syndrome (Buchen, Frood 2008, 2012, Mithoefer et al 2011, 2012, Oehen). However research still shows a degree of potential long-term change that is cause for caution.

MDMA acts as a "releasing agent" of serotonin, norepinephrine, and dopamine (Partilla et al, Verrico et al). It enters neurons via the monoamine transporters. Once inside, MDMA inhibits the vesicular monoamine transporter, which supplies dopamine in vesicles as a function of pre-synaptic neuron excitation. This results in increased concentrations of serotonin, norepinephrine, and dopamine in the cytoplasm and enhances their release by reversing their respective transporters through phosphorylation. The releasing agent blocks the presynaptic cell's ability to use the vesicular transporter to package neurotransmitters into vesicles. The result is increased neurotransmitter release that is not dependent on the phasic activity of the presynaptic cell. MDMA has been identified as a potent agonist of TAAR1, trace amine-associated receptor 1, a G protein-coupled receptor located on the presynaptic membrane. Activation of TAAR1 inhibits transporter function via cAMP. These effects increase monoamine efflux and prolong the amount of time monoamines remain in the synapse.

MDMA also acts as a weak 5-HT1 and 5-HT2 receptor agonist, and its more efficacious metabolite MDA (7% of MDMA becomes MDA) likely augments this action. Its unusual entactogenic effects may be partly due to oxytocin secretion (Young), which facilitates bonding and the establishment of trust via agonizing the serotonin 5-HT1A receptor. A placebo-controlled study in 15 human volunteers found that 100 mg MDMA increased blood levels of oxytocin, and the amount of oxytocin increase was correlated with the subjective prosocial effects of MDMA (Dumont et al 2009). MDMA may also act by increasing ventromedial prefrontal activity and decreasing amygdala activity, which may improve emotional regulation and decrease avoidance, and by increasing norepinephrine release and circulating cortisol levels, which may facilitate emotional engagement (Johansen & Krebs).

Because it acts on transporters, MDMA causes a reduction in the concentration of serotonin transporters (SERTs) in the brain. Animal studies have demonstrated lasting serotonergic changes, but other studies suggest the process is reversible. Immediate depletion of serotonin in the days following Ecstasy use can be significantly alleviated by consumption of 5-hydroxy-tryptophan an immediate serotonin precursor. In an animal study an MDMA dose reducing serotonin levels below 35-50% were improved to 66-85% on 5-HTP supplementation (Wang et al). Two studies also suggest possible heart valve defects (see section 10).

For the first time a study supported by UK Channel 4 and followed by New Scientist is investigating live human brain scans on MDMA, prevented up till now by restrictions on research (Lawton 2012, White).

Some human studies show MDMA may be neurotoxic (Reneman), however others suggest that any potential brain damage may be at least partially reversible following prolonged abstinence (Baggott, & Mendelson). The relevance to humans of animal studies on rodents documenting neurotoxic damage caused by MDMA is unclear, as different species metabolize drugs differently and at different rates (Baumann, de la Torre & Farre). The causes of neurotoxicity also remain unclear. Several studies have indicated a possible mechanism, through the reaction of α-methyldopamine, a principal metabolite, and glutathione, the major antioxidant in the human body. One possible product of this reaction, 2,5-bis-(glutathion-S-yl)-alpha-methyldopamine, has been demonstrated to produce the same toxic effects observed in MDMA (Miller et al), while MDMA, and alpha-methyldopamine have been shown to be non-neurotoxic (McCann & Ricaurte). Various metabolites of MDMA may interfere with the mitochondrial electron transport system, leading to increased leakage of reactive oxygen species (ROS) from the mitochondria. ROS and catalytic cycles of P450-mediated MDMA metabolism may oxidatively modify cellular macromolecules such as lipids, DNA, and proteins (Song et al).

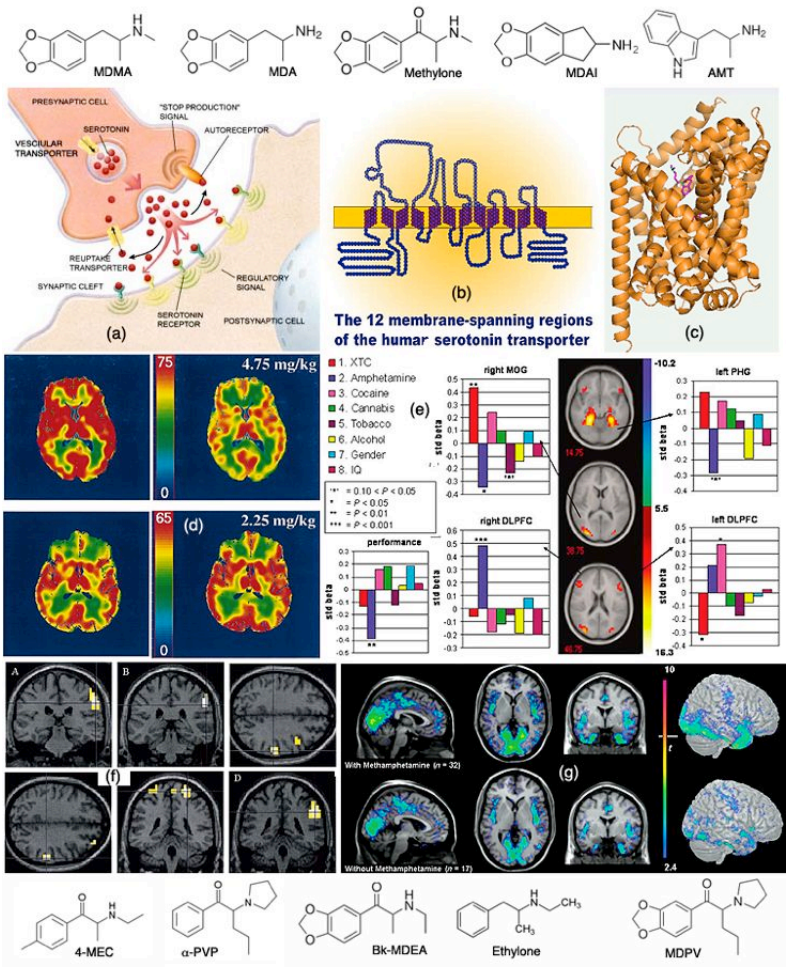
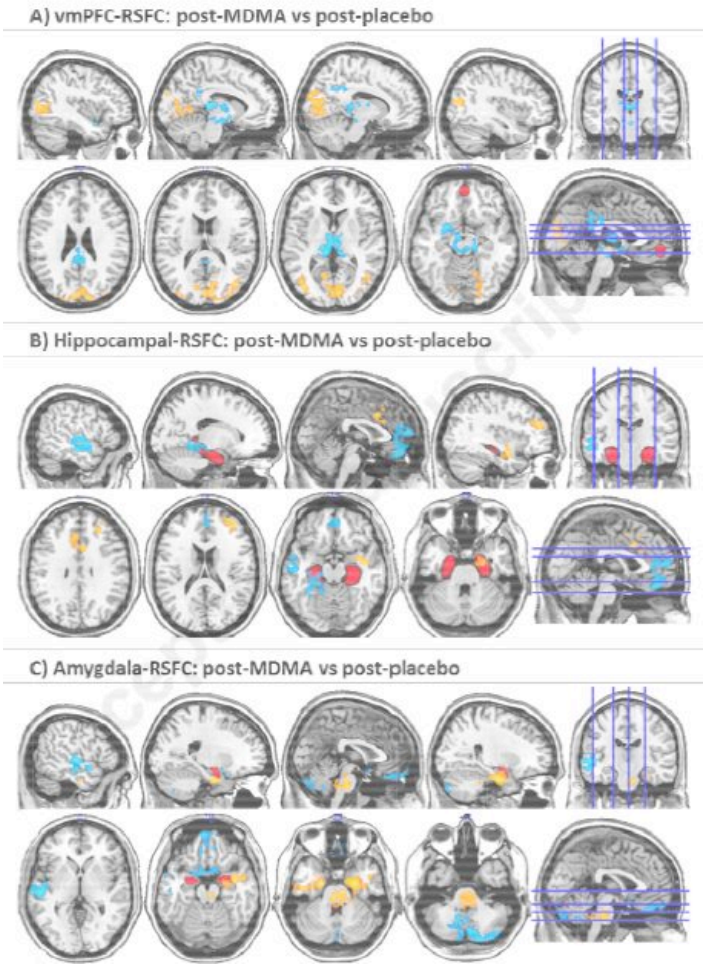


Fig 20: (Top) Entactogens **(a)** The role of the transporter in the synapse, **(b,c**) 2D and 3D structures of the serotonin transporter SERT **(d)** Levels of serotonin at Ecstasy dose and 3 weeks after for low and high doses (Chang et al 2000) **(e)** Comparable enhancement of activation in various brain areas under several psychotropic agents suggests MDMA causes hyperexcitation (Jager et al) **(f)** A study comparing MDMA users against controls for differences in brain function (Daumann et al). **(g)** Decrements in serotonin transporter density with MDMA use (above) with and (below) without concurrent methamphetamine use (Kish et al). (Bottom) Undesirable consequences of banning MDMA. Four molecules, 4-MEC, Bk-MDEA, ethylone, and α-PVP found together in pills marketed as MDMA, intrinsically more dangerous than MDMA itself (Savage). MDPV, also called 'bath salts', presents another party drug substitute for MDMA, notorious for violent incidents, which is a nor-epinephrine and dopamine reuptake inhibitor, resulting in hypervigilance attacks. One person was reported as disembowelling himself and throwing his intestines at police trying to subdue him (Campbell).

Many of the reported deficits associated with MDMA may actually result from concurrent use of other party drugs, including stimulants such as amphetamines (Kish et al). Methamphetamine is a potent dopamine releasing agent with lesser effects on norepinephrine and serotonin, which is a known neurotoxin, shown to cause dopaminergic degeneration. When dopamine breaks down, it produces reactive oxygen species. It is likely that the approximate twelvefold increase in

dopamine levels and subsequent oxidative stress that occurs after taking methamphetamine mediates its neurotoxicity. Dopamine oxidation, particularly close to synaptic vesicles, produce oxidative stress that in turn leads to exacerbation of autophagy that can destroy axons and dendrites (Larsen et al).

In a first for legitimate drug research into the actual effects of entactogens, a team led by Nutt and Carhart-Harris has used f-MRI to investigate the effects of MDMA on volunteers (Carhart-Harris et al 2013). They note that MDMA decreases cerebral blood flow (CBF) in the right hippocampus and amygdala, the visual cortex, pre-supplementary motor area, superior frontal gyrus and primary somatosensory cortex. They note that decreased hippocampal-ventromedial prefrontal cortex coupling predicts intense and euphoric effects after MDMA and that decreased right amygdalal and hippocampal CBF predicts intense subjective effects after MDMA.



MDMA was orally administered to 25 physically and mentally healthy individuals in a double-blind, placebo- controlled, balanced-order study. Arterial spin labelling (ASL) and seed-based resting state functional connectivity (RSFC) were used to produce spatial maps displaying changes in cerebral blood flow (CBF) and RSFC after MDMA. MDMA produced marked increases in positive mood. Only decreased CBF was observed after MDMA and this was localised to the right medial temporal lobe (MTL), thalamus, inferior visual cortex and the somatosensory cortex. Decreased CBF in the right amygdala and hippocampus correlated with ratings of the intensity of MDMA's global subjective effects. The RSFC results complemented the CBF results, with decreases in RSFC between midline cortical regions, the medial prefrontal cortex and MTL regions, and increases between the amygdala and hippocampus. There were trend-level correlations between these effects and ratings of intense and positive subjective effects.

Toxicity and entactogenic effects of MDMA may depend to some extent on the two chiral versions of the molecule. (S)-MDE produced elevated mood, impairments in conceptually driven cognition and marked right frontal activation. In contrast, (R)-MDE produced increased depression, enhanced visual feature processing, and activation of visual cortical and left frontal areas. Plasma concentrations were higher for the (R)-enantiomer. The so-called entactogenic effects of MDE are likely to be caused by the (S)-enantiomer, whereas (R)-MDE appears to be responsible for neurotoxic effects (Spitzer et al). It is possible anti-oxidants might help alleviate this. The effects may also vary significantly between the sexes (Allott & Redman). Two studies have also found changes in hormone expression (Gerraa et al), and emotional facial recognition (Hoshi et al 2004), with ACTH and cortisol levels higher but more blunted under stress in Ecstasy users, and heightened ability to recognize fearful facial expressions on day 0 but reduced capacity on day 4, suggesting lowered serotonin.

Depression (Falck et al., Verheyden S. et al) and deficits in memory have been shown to occur more frequently in long-term MDMA users (Ainsworth, Lawton 2009). The most pronounced effects are on associative and prospective memory. Focused attention, the ability to zoom in quickly on a new task is affected, though sustained attention is not. The difficulty with these studies is removing confounding factors. Ecstasy use varies from occasional single tablets to bingeing on up to ten at a time (Parrot 2005), and Ecstasy users are also frequently multiple drug pill users, often taking stimulants such as amphetamines as well, which are known to cause significant detriments. Furthermore it remains uncertain exactly what is actually in underground tablets, which often contain other ingredients, and not MDMA.

Serotonin functions to smooth connections between the prefrontal cortex (ventral anterior cingulate cortex and ventrolateral PFC) and amygdala involved in processing anger, and serotonin depletion has also been shown to affect respnses to perceived anger and promote impulsive aggression (Passamonti et al).

De Win et al (2007) note the degree of controversy and scientific inconsistency in the ongoing research: "There is increasing evidence that Ecstasy is toxic to the human brain, especially to the serotonergic system, although the validity of these findings is still highly debated (Turner and Parrott, Grob, Kish). Many human studies are littered with methodological problems, including inadequate sampling of subjects and controls, lack of drug use analysis, and lack of baseline data."

Consistent with these confounding variables, a study of neurocognitive function (Hoshi et al 2007) found recreational drug use in general, rather than Ecstasy use per se, can lead to subtle cognitive impairments and that recent drug use appears to impact most strongly on cognitive performance.

Some studies claim a consistent decrement in performance with increasing Ecstasy use. One review (Zakzanis et al) found small-to-medium effects across all cognitive domains with learning and memory being most impaired and that total lifetime ingestion of MDMA appeared to be negatively associated with performance on tasks ranging from attention and concentration to learning and memory. In another 'meta-analysis' (Varbaten et al) ecstasy users had lower verbal short and long term memory scores, reacted more slowly and made more errors. However the meta-regression coefficients were not significant, indicating no support for a linear relationship between the mean effect size values and total lifetime Ecstasy exposure, raising questions over whether it was Ecstasy use or confounds causing the effect.

In two other studies (Montgomery et al, Wareing et al) Ecstasy users performed worse than nonusers, in the former on all, and in the latter on some cognitive measures. However in another study (Fisk et al), Ecstasy users were unimpaired on all measures of random generation performance although Ecstasy users scored significantly lower on one test, the computation span measure.

A low dose study, (Schlilt 2007, 2008) found initial Esctasy use (mean 3.2 tablets) had a significant dose-related negative effect on verbal delayed recall after adjusting for the use of other drugs, suggesting that even a first low cumulative dose of Ecstasy can be associated with decline in verbal memory, although the performance of the group of Ecstasy users is still within the normal range and the immediate clinical relevance of the observed deficits is limited.

In a study of prospective memory, remembering to do things on a delayed schedule (Rendell et al), Ecstasy users were significantly impaired irrespective of the task demands, after controlling for marijuana use, level of psychopathology, and sleep quality, but not apparently for other drugs such as methamphetamine. Parrott (2006) has suggested that cannabis might offset some of the acute and toxic effects of MDMA. A second study of prospective memory (Rodgers et al) gave conflicting results. An association was found between the lifetime use of ecstasy and self-reported difficulties in long-term prospective memory for some ecstasy users. However participants accessing the research via an ecstasy-related bulletin board showed no association between long-term prospective memory and use of ecstasy, and any association was markedly reduced when nicotine and cannabis were included as covariates. The researchers suggest nicotine may have been a confounding factor.

In a series of brain scan studies designed to complement direct tests of competency, two studies (Bauernfeind et al, Jager et al) found evidence of increased cortical excitability in Ecstasy users completing a cognitive task. The latter found use of Ecstasy had no effect on working memory and attention, but drug use was associated with reduced associative memory performance. Multiple regression analysis showed that associative memory performance was affected by amphetamine much more than by Ecstasy. An fMRI investigation of motor function (Salomon et al) suggested prior MDMA use was associated with BOLD deficits in coherence and connectivity, among motor pathways, but one would imagine any significant effects being noticeable to the subjects and reported in the medical literature.

A pair of studies (de Win et al 2007, 2008) explored specific changes in rrCBV - relative regional blood volume; FA - fractional anisotropy of the diffusional motion of water molecules in the brain, which gives an indication of axonal integrity; and ADC - apparent diffusion coefficient. In the first study comparing first Ecstasy users after 2 weeks with non-users, a variety of metabolic tests were normal and after correction for multiple comparisons, only the rrCBV decrease in the dorsolateral frontal cortex remained significant. In the second study, which also compared novel low-dose ecstasy users (mean 6.0, median 2.0 tablets) to

non-users, showed decreased rrCBV in the mid brain globus pallidus and putamen; decreased FA in thalamus and fronto-parietal white matter; increased FA in the globus pallidus and increased ADC in the thalamus. No changes in serotonin transporter densities and brain metabolites were observed. These changes, although subtle, do suggest sustained effects of ecstasy on brain microvasculature, white matter maturation, and conceivably, axonal damage due to low dosages of ecstasy.

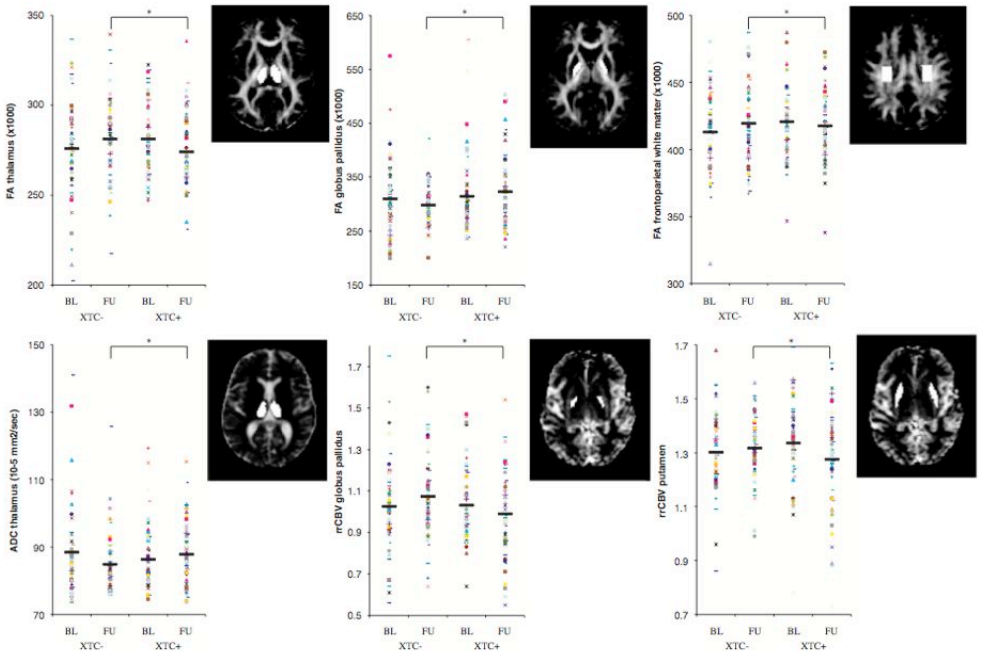


Fig 21: Changes in FA, rrCBV and ADC (de Win et al 2008) at baseline (BL) and follow up (FU). These changes are very moderate, but so is the consumption (de Win et al 2008).

However other brain studies show only marginal differences and/or signs of long term recovery to norms. In a study examining blood distribution volume ratio (Buchert et al), this was significantly reduced in the mesencephalon and the thalamus in Ecstasy users. However in former Ecstasy users it was very close to drug-naive control subjects in all brain regions, suggesting recovery. In another study examining cerebal blood flow (Chang et al 2000) abstinent MDMA users showed no significantly different global or regional CBF compared to the control subjects. However, within 3 weeks after MDMA administration, regional CBF remained decreased in several areas compared to baseline and was markedly more pronounced in subjects who received the higher dosage of MDMA. Likewise a study of Ecstasy users (50+ tablets) two weeks after abstinence showed reduced SERT binding in the occipital cortex (Schouw et al).

In a study in which subjects were given a working memory performance task and given fMRI sacns (Daumann et al), there were no significant group differences in working memory performance and no differences in cortical activation patterns for a conservative level of significance, however, for a more liberal criterion, both user groups showed stronger activations than controls in right parietal cortex, and, heavy users had a weaker blood oxygenation level-dependent (BOLD) response than moderate users and controls in frontal and temporal areas. The effects were thus relatively minor but suggestive.

In studies in which more rigorous attempts have been made to remove confounding factors, the deficits in cognitive function reported for MDMA tend to disappear.

One study (Bedi & Redman) assessed 45 currently abstinent Ecstasy polydrug users, 48 cannabis polydrug users and 40 legal drug users. Standardized neuropsychological tests were used to measure attention, verbal, visual and working memory and executive function. Prospective memory function was also assessed. It was not possible to discriminate between groups on the basis of the cognitive functions assessed. Although the results suggest that heavy use of Ecstasy is associated with some lowering of higher-level cognitive functions, they do not indicate a clinical picture of substantial cognitive dysfunction.

A second study (Halpern et al) designed to minimize limitations found in many prior investigations, in particular minimal exposure to other drugs, failed to demonstrate marked residual cognitive effects in Ecstasy users. The authors comment: “This finding contrasts with many previous findings - including our own - and emphasizes the need for continued caution in interpreting field studies of cognitive function in illicit Ecstasy users.”

Halpern is sharply critical of the quality of the research that has linked ecstasy to brain damage: “Too many studies have been carried out on small populations, while overarching conclusions have been drawn from them,” he said. For a start, some previous research has studied users who were taken from a culture dominated by all-night dancing, which thus exposed these individuals to sleep and fluid deprivation - factors that are themselves known to produce long-lasting cognitive effects. Non-users were not selected from those from a similar background, which therefore skewed results. In addition, past studies have not taken sufficient account of the fact that ecstasy users take other drugs or alcohol that could affect cognition or that they may have suffered intellectual impairment before they started taking ecstasy. In Halpern's study only ecstasy users who took no other drugs and who had suffered no previous impairment were selected (McKie).

9: Doors of Delirium: Scopolamine and Muscarinic Acetyl-choline Antagonists

Muscarinic acetyl-choline antagonist deliriants have been used for centuries, both as hallucinogenic agents in medieval Europe, Asia and Native American cultures, and in rites of passage of manhood to forget childhood, as well as for criminal and military purposes.

Although they have been sporadically used recreationally, their severe effects of anterograde and temporary global amnesia combined with delirious and often manic behaviour and panoramic hallucinations which the subject confuses with reality, talking to non-existent people and engaging with imaginary spectacles, often also accompanied with unconsciousness and coma, leave these agents off the spectrum of legitimate entheogens, except for the continuing evidence of their cultural use.

Scopolamine, despite its severe hallucinogenic and amnesiac properties, is used in minute quantities for motions sickness, for treatment of addiction and as an anti-depressant (Furey & Drevits). Hyoscyamine is the active chiral component of atropine an essential WHO core medicine. The belladonna genus Atropa is named after one of the three Greek fates, who chose how a person was to die. It has been used historically as an anaesthetic, to dilate the pupils to make women more attractive (bella donna) and to commit murder, as evidenced by the actions of the wives of Augustus and Claudius. Four second-hand accounts of its acutely disabling and dangerous affects are included in the case study.

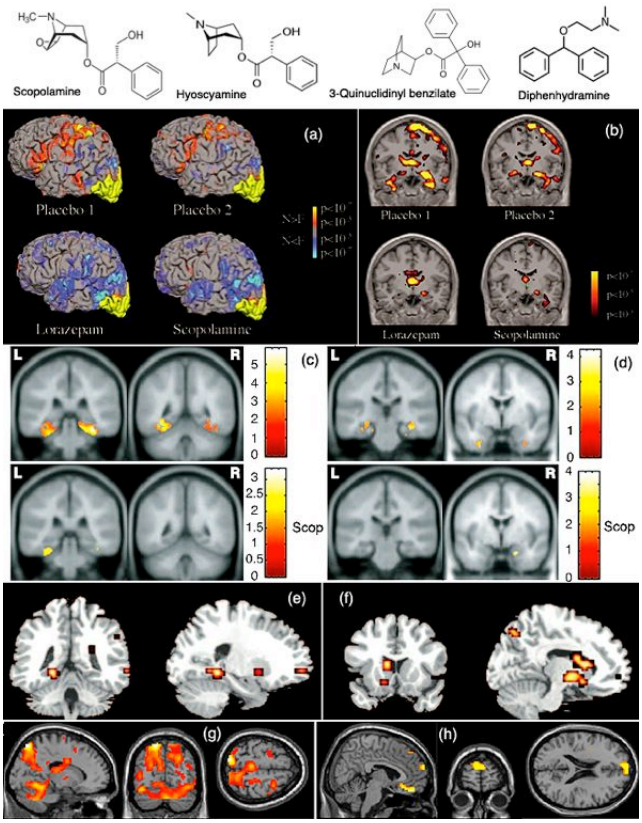


Fig 22: (Top row) four hallucinogenic deliriants. Scopolamine and hyoscyamine are present in Datura, and Brugmansia species and related solonaceous plants such as belladonna (deadly nightshade), henbane and mandrake. 3-Quinuclidinyl benzilate is a chemical warfare incapacitating agent also called BZ. Diphenhydramine (benadryl) is an anti-histamine which also has muscarinic acetyl-choline antagonist activity. (a,b) Reduction of cortical and hippocampal activation under scopolamine novel face-name pairs vs. fixation, for diazepam and scopolamine (Sperling et al). (c) Right and left hippocampal inactivation under scopolamine under active maintenance analysis (d) match and non-match memory tasks also showing hippocampal inactivation (Schon et al)). (e,f) Hippocampal inactivations and striatal activations under scopolamine in a spatial memory task (Antonova et al). (g,h) Inactivations and activations under scopolamine during a memory task matching 2 images back (Voss et al). All of these studies used a moderate 0.4 mg dose of scopolamine by injection.

Early in the 20th century physicians began to employ scopolamine, along with morphine and chloroform, to induce a state of "twilight sleep" during childbirth. Yet physicians noted that women in twilight sleep answered questions accurately and often volunteered exceedingly candid remarks. In 1922 Robert House, a Dallas obstetrician, arranged to interview under scopolamine two prisoners in the Dallas county jail whose guilt seemed clearly confirmed. Under the drug, both men denied the charges on which they were held; and both, upon trial, were found not guilty. Enthusiastic at this

success, House concluded that a patient under the influence of scopolamine "cannot create a lie ... and there is no power to think or reason." His experiment and this conclusion attracted wide attention, and the idea of a "truth" drug was thus launched upon the public consciousness, although barbiturates later came to be more of a drug of choice in interrogation (Bimmerle). Nevertheless scopolamine like drugs, including 3-quinuclidinyl benzilate and n-ethyl-3-piperidyl benzilate continued to be developed as incapacitating chemical warfare agents.

Following World War II, the United States military investigated a wide range of possible nonlethal, psychobehavioral chemical incapacitating agents to include psychedelic indoles such as LSD-25, marijuana derivatives, certain tranquilizers like ketamine or fentanyl, as well as several glycolate anticholinergics. Copious amounts of phencyclidine are also documented as having been tested on active military personnel such as in the Edgewood Arsenal experiments. One of the anticholinergic compounds, 3-quinuclidinyl benzilate, was assigned the NATO code BZ and was weaponized at the beginning of the 1960s for possible battlefield use. BZ was invented by Hoffman-LaRoche in 1951. In 1959 the United States Army began to show interest in using the chemical as a chemical warfare agent. The agent commonly became known as "Buzz" because of this abbreviation and the effects it had on the mental state of its casualties. In February 1998, the British Ministry of Defence accused Iraq of having stockpiled large amounts of a glycolate anticholinergic incapacitating agent known as Agent 15, chemically either identical to BZ or closely related to it.

Scopolamine has also been used criminally as a poison or spray that can incapacitate a person, or cause them to become obedient to a criminal's intent. In Colombia the criminal administration of Datura or Brugmansia extracts, known as Burundanga, appeared during the 1950s. In the early 1980s, pure scopolamine began to be used. In a Colombian city of 500,000 people around 100 cases were reported in 1980-81. In one instance, a young professional woman was approached by a man, who possibly sprayed her face, resulting in her becoming docile, going to work inebriated and withdrawing her salary, her money from ATMs and her jewelry from her apartment and giving it to her assailant before lapsing into amnesiac somnolence. In hospital, scopolamine and fenotiazine were found in her urine (Ardila & Moreno).

Learning and memory (Deutsch) as well as attention and processing speed are critically modulated by the cholinergic neurotransmitter acetylcholine. Dale in 1914 showed that acetycholine acts at two pharmacologically different receptors, nicotinic, which form ligand-gated ion channels and muscarinic, which are G protein coupled. Muscarinic receptors represent the majority of cholinergic brain receptors. The neocortex has a mixed muscarinic population with 67% M1 receptors, with high affinity for pirenzepine and 33% M2 muscarinic receptors. Hyoscyamine (atropine) and probably scopolamine are M1 antagonists. Increase in the number of muscarinic receptors in the hippocampus of rats has been observed as a consequence of long-term scopolamine administration (Ardila & Moreno). The cholinergic system constitutes one of the most important transmission systems for mediating cognitive processes in humans, with cholinergic projections originating in the nucleus basalis of Meynert and the substantia innominata in the basal forebrain, which has wide projections across the neocortex. By projecting to the hippocampus and to frontal areas, they mediate fundamental cognitive processes (Voss et al).

Studies utilizing scopolamine to examine the effects on cognition have consistently shown that it impairs cognitive functions like learning, memory, verbal fluency and attention. Alzheimer’s and schizophrenia patients present cognitive deficits while at the same time exhibiting specific alterations of the cholinergic system as evidenced by post-mortem studies. Early studies in India on monkeys smoking cannabis and datura suggested that datura alkaloids cause brain shrinkage while cannabis does not. Virtually all the brain scan research cited focuses on using scopolamine as an experimental drug in learning about memory impairment, emphasizing its major impact on memory.

10: Safety Considerations of Psychedelic Use and Global Drug Policy

The potential long-term health effects and risks of NMDA antagonists, cannabinoids and entactogens have already been extensively discussed. We now turn back to the classic psychedelics. By all measures, as noted in fig 23, psychedelics, even the unpredictable genie in the bottle LSD, do not have evidence of long-term physical damage and rank far below legal alcohol and tobacco as socially or physically damaging agents. Case reports of long-term psychiatric problems attributed to LSD, include psychosis, panic attacks, other anxiety disorders, and depression. There are very few case reports of prolonged psychiatric symptoms following psilocybin or mescaline. However any long term case reports now look to be due to the coincidental incidences of mental illness unrelated to psychedelic use. In a study of 130,152

respondents, randomly selected to be representative of the adult population in the US, 21,967 of which (13.4% weighted) reported lifetime psychedelic use, there were no significant associations between lifetime use of any psychedelics, lifetime use of specific psychedelics (LSD, psilocybin, mescaline, peyote), or past year use of LSD and increased rate of any of the mental health outcomes. Rather, in several cases psychedelic use was associated with lower rate of mental health problems (Krebs & Johansen).

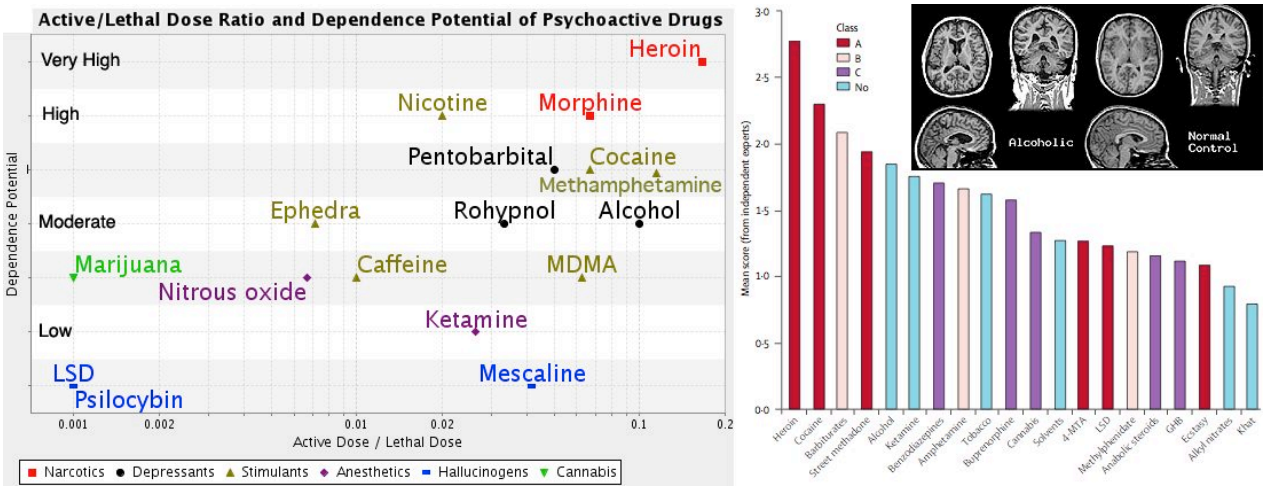


Fig 23: Relative safety of a spectrum of psychoactive drugs (left) in terms of dependence versus active/lethal dose (Wikipedia) and (right) in terms of several measures of relative harm (Nutt et al). In both perspectives psychedelics rate as very safe and having harm potential decisively below legal drugs alcohol and tobacco. (Top right) Putative effects of alcoholism on an MRI scan, showing enlarged ventricles and a shrunken brain.

This cannot be said for street drugs, even some of those purchased over the internet, or for the more savage members such as the fly series, which have toxic or lethal effects not far above the active dose. A Danish man whose friend died on bromodragonfly had this to say of it: “It was like being dragged to hell and back again. Many times. It is the most evil [thing] I've ever tried. It lasted an eternity”. Most serotonin agonists also have peripheral, including vasoconstrictor, effects. Virtually all psychedelics and entactogens have strong 5HT2b binding. Prolonged use in the case of some 5HT2b agonist and serotonin releasing pharmaceutical drugs, such as fenfluramine, have resulted in heart valve anomalies (Rothman et al, Roth 2007, Schade et al, Zanettini et al), and entactogens MDMA and MDA have also been shown to have similar effects (Setola et al, Droogmans et al). Some psychedelics also cause such effects, but only permit intermittent use. Binding of ergotamine and to a lesser extent LSD to 5HT2b receptors invokes the β-arrestin pathway over G-protein signalling (Wang et al, Wacker et al).

I will here focus on the natural psychedelics and in particular psilocybin of sacred mushrooms, but many of the same considerations apply to mescaline bearing cacti and ayahuasca. Although sacred mushrooms were pejoratively claimed to cause premature senility in apocryphal earlier accounts, there is no evidence psilocybin, sacred mushrooms, mescalin cacti, or ayahuasca cause long-term physical harm. Both my peyote roadman Tellus Goodmoring and Maria Sabina the mushroom curandero lived well into their nineties and Senor Trinico the brujo I first took ayahuasca with remained in good heath when I visited him 20 years after my first experience, despite being in remission from leprosy.

The physical side effects resulting from psilocybin consumption are generally not considered significant. Nausea and vomiting can occur, particularly with wild mushrooms, which can contain bacteria, or be partly spoiled. High and or low blood pressure changes can sometimes result in fainting. Other adverse effects less frequently reported include panic attacks, paranoia, confusion, derealization, disconnection from reality, mania, and isolated cases of temporary paralysis and cardiac malfunction after eating less common forest species (Yokoyama, Borowiak et al). Neither flashbacks, nor hallucinogen persisting perception disorder, are commonly associated with psilocybin usage (Carhart-Harris & Nutt) as they have been with LSD (Abraham & Duffy). Unsurprisingly, usage by those with schizophrenia can induce acute psychotic states. A 2010 study on the short- and long-term subjective effects of psilocybin administration in clinical settings concluded that despite a small risk of acute reactions such as dysphoria, anxiety, or panic, “the administration of moderate doses of psilocybin to healthy, high-functioning and well-prepared subjects in the context of a carefully monitored research environment is associated with an acceptable level of risk” (Studerus et al). All of these show that use of hallucinogens should be undertaken only in a protective environment where there are people able to look after individuals and protect them from immediate harm.

In addition to the beneficial effects of mystical-type experiences (Griffiths et al) already reported, a pilot study (Vollenweider & Geyer) found that the use of psilocybin was associated with substantial reductions in OCD symptoms, possibly caused by psilocybin's ability to reduce the levels of the serotonin-2a receptor. In a second study (Sewell et al), half of patients with cluster headache, often considered not only the most painful type of headache, but "one of the worst pain syndromes known to mankind," reported that psilocybin aborted the attacks, and most reported extended remission periods. Preliminary results indicate that low doses of psilocybin can improve the mood and reduce the anxiety of patients with advanced cancer, and that the effects last from two weeks to six months (Vollenweider & Geyer).

There are thus no scientific grounds to continue to ban the use of entheogens, particularly those of a natural origin, nor to incarcerate people for long periods for consuming or possessing them. Safe and comfortable protected social contexts for use with sane guidance need to be developed. Sacred mushrooms, peyote and ayahuasca are intrinsically safer than either street drug phenylethylamines (which can have lethal consequences, when the drug is impure, or the dosages are confused), or LSD (which had some very unpredictable consequences among our friends in the 1970s, including a bout of amnesia lasting several days, a psychotic episode lasting a month, and an acute manic break requiring physical restraint followed by coma perceived later as a rebirth experience).

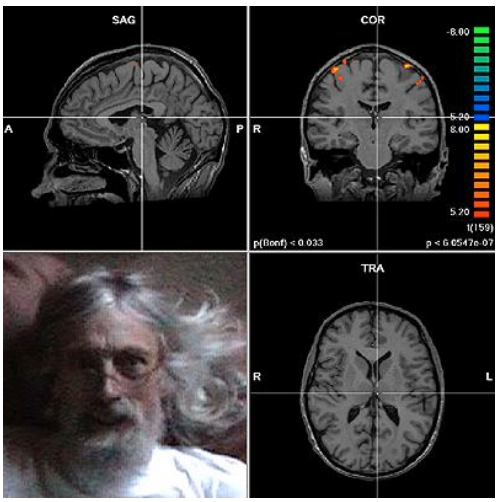
(Left): Real time clock of costs of the War on Drugs for the year, of $30.6 billion (http://www.drugsense.org/cms/). (Right: Three organizations promoting research and policy reform Global Commission on Drug Policy (http://www.globalcommissionondrugs.org/), Multidisciplinary Association for Psychedelic Studies (MAPS) (http://www.maps.org/), and the Hefter Research Institute (http://www.heffter.org/). The War on drugs costs around $30 billion annually. While the world invests billions in scientific discovery, it wastes much greater sums preventing discovery of alternative conscious states. Compare this with an overall budget of $7 billion for the Large Hadron Collider and $3 billion for the Human Genome Project. If half the money spent in the War on Drugs were dedicated instead to public education and health it would be more than enough and leave $15 billion a year in surplus for research and discovery - two LHCs per annum! A tiny fraction of this would be enough to fund psychotropic research into the foundations of consciousness.

More generally, the war on drugs, based on prohibition, incarceration, and capital punishment, even when applied to manifestly more dangerous drugs, such as morphine, heroin, cocaine and methamphetamine simply feeds militant gang violence and fosters uncontrollable global criminal enterprise. It is extremely costly in terms of broken familes, soaring murder rates and dangerous impure street drugs. The International Centre for Science in Drug Policy in its 2013 report (Werb et al) concludes the war on drugs has failed. Illegal drugs are now cheaper and purer globally than at any time over the last 20 years. The report said street prices of drugs had fallen in real terms between 1990 and 2010, while their purity and potency had increased. In Europe, for example, the average price of opiates and cocaine, adjusted for inflation and purity, decreased by 74% and 51% respectively between 1990 and 2010 accompanied by a substantial increase in most parts of the world in the amount of cocaine, heroin and cannabis seized by law enforcement agencies. It concluded: "These findings suggest that expanding efforts at controlling the global illegal drug market through law enforcement are failing."

This failed strategy is a corrupt pawn of political expedience and urgently needs to cease in favour of an attitude of public health for those suffering from abuse and respect for the rights of individuals to make autonomous decisions about their altered states in a safe setting (Carlsen, Jahangir et al, Nutt et al, Torrens & Ruiz-Goirena, Travis, White). The paradox of the situation is emphasized by the virtual impregnability of the drug market Silk Road behind the Tor anonymizer which is in turn partly funded by the US government free internet initiative (Ball http://www.guardian.co.uk/world/2013/mar/22/silk-road-online-drug-marketplace). For an excellent documentary focused on the Global Commission on Drug Policy, see: Breaking the Taboo http://www.breakingthetaboo.info/. See also: Q&A: Mexico's drug-related violence http://www.bbc.co.uk/news/world-latin-america-10681249, US marijuana legalisation fuels Mexico drugs

war debate http://www.bbc.co.uk/news/world-latin-america-20397335, The trouble with using police informants in the US http://www.bbc.co.uk/news/magazine-21939453.

11: An Across-the-Spectrum Case Study



To round off this investigation, I am going to include a case study in the first person. No matter how much investigation goes into understanding the properties of entheogens, they remain *sine qua non* agents of transformation of subjective consciousness, which need to be understood in the subjective. Short of readers experiencing these agents for themselves, the closest we can come to an understanding is through first-hand subjective reports. First person accounts, although they are once-removed, can give a far deeper description of the changes induced by these substances than brain scans, or EEGs can. So in the interests of a more enlightened approach to entheogens, in parallel with writing this paper, and as the original inspiration to write it, I have made a spectral investigation, sampling the conscious states key members of these agents invoked in my own consciousness. At the age of 67, in tender retirement, I also feel I owe it to younger generations to test out what they are doing to themselves and pass some sort of judgment on the diverse mind-altering agents in common currency.

I will thus discuss the subjective effects of the classic psychedelic psilocybin (sacred mushrooms), the entactogen MDMA (Ecstasy), a selective 5HT2a agonist n-benzyl-phenylethylamine psychedelic (25C-NBOMe), the dissociative anaesthetic ketamine, and salvinorin-A in terms of their capacity to induce a full-blown entheogenic experiences. Each experience is written as an account to my sister who hasn't tried any of these agents to explain some features of the experience that struck me in the evening afterwards. There is one dreaming account during the time of these case studies to examine provocative anticipatory features of dreaming consciousness. To gain an idea of the severe effects of muscarinic acetyl-choline antagonists such as scopolamine, which I have never been prepared to try, I have included three medieval accounts and a current one.

As noted, I have also taken mescalin in the form of San Pedro, and peyote in a traditional peyote meeting at Taos Pueblo with the roadman Tellus 'Goodmorning' and on the peyote fields of el Catorce Real in Mexico, sacred mushrooms at Palenque, DMT and harmine in the form of ayahuasca with Senor Trinico at Yarinacocha, Pucallpa in Amazonian Peru (see fig 3), and experimented with psilocybin containing sacred mushrooms, potentiated by the natural monoamine oxidase inhibitor harmaline, with DMT and cannabis in combination, as well as pure LSD in the days of orange sunshine, so have a reasonably comprehensive familiarity with psychedelic entheogens. For 40 years I have confined myself to natural sacred species to avoid the impurities of street drugs and follow traditions of cultural use established and respected over millennia, so this is also an exploration into a diversifiying field of designer synthetics.

Sacred Mushrooms and Psilocybin

A couple of days ago, for the first time in a year and a half, because, like most people, I am habitually fearful of my mind being torn apart by visionary transcendence, I persuaded myself to imbibe a powerful whack of the very best crisp dried sacred mushrooms, as a devotional meditation, lest the passage of the years carry me unrequited ever closer to the edge of dissolution, before I have fulfilled my covenant with destiny. As the great wave of reverie broke over me, they gave me an overflowing and integrated vision of how cosmic consciousness comes about in the universe, in one of the cleanest, and yet strongest, spiritual experiences I have had, totally restoring my sense of psychic vitality and meaning, as they have done countless times in younger days, as the sheet-sail for my tortuous journey through life.

Real religious sacraments have to be able to be powerful enough agents to be able to transport us into the *mysterium tremendum*. They also require meditative vigil to enter deeply into the experience. I try to retreat into reflective solitude, without thought processes, or internal dialogue, lying watchfully, with eyes sometimes open and sometimes closed, and often half-open and half-closed, as the Buddha is depicted as doing, tuning consciousness with my breathing into a resonant state of attention, sensitive to the ensuing visionary miasma. I begin lying quietly and over about twenty minutes I can begin to feel the effects coming on. Often I feel anxious and restless before the peak, something I am coming to associate with the possible effect of the 2c receptor, and I note Griffith's statement that a key to gaining a

positive experience for his study participants, depends on getting just the right dose. This time I have measured just 1.3 grams of very crisp dried psilocybe shoots, and this proved to be an ideal dose in the company of a mild measure of cannabinoids. The first real effects if I am lying quietly are a combined synesthesic rush of pattern and sound that often rises almost to a shrieking peak as the first wave strikes. If I let go of my surroundings I can fall into or flow into these resonant patterns, so they become visions and experiential spaces utterly different from the waking world, as if I am not only witnessing my brain generating consciousness but the nature of disembodied consciousness in the bardo.

Dilated pupil on an earlier session of psilocybin with harmaline.

I won't go into all the incidental details of the retinal circus, the complex dynamically interlacing 3-D fibers and fractals, their rushing vortices and echoing currents, of entering many interconnected layers of dreaming and waking reality, or even a vision of being transported to join God in heaven, with Saint Peter ushering me in on a comic stage vibrating like a New Orleans carnival. The key is the overwhelming power, truth, beauty and integrity of the experience, convincing me in its full intuitive detail, yet again, that the living sacraments contain the genuine royal blood, or *sang raal*, route to religious knowing, beneficial to all life. This is a state that seems to emerge out of the entheogenic experience as a fully integrated knowledge, or gnosis. It is not something you can put together philosophically or explain in terms of its details and it can't be taken back in its entirety to the everyday world, except as an enchanted memory and a source of life-enhancing wisdom.

By entering into the entheogenic state of reverie without thought in a meditative calm, one enters a state where there is a resonance with the patterns and sounds, which one can fall into, and once one does, it is as if one has entered another reality, as different from waking life as dreaming is, with its own existential implications, one of which is gnosis about the flow of life, the meaning of life, and the sense of one's ego dissolution, in becoming one with the conscious process that drives all sentient life in the universe. It is a state of being amid the patterns in the stillness of the conscious void that is evidentially true, palpable, felt at once in one's emotions and in the stillness of one's mind. By the same connection I inherit a personal responsibility to unfold this experience for others, for the sake of life and the planetary future. Of course one can take sacred mushrooms recreationally and have an adventurous experience, but for me it is like returning home to a place where I become my true self, and navigate my life with some grace and insight, as one takes an intercontinental sailing journey across the Styx between birth and our eventual demise.

Ecstasy ('MDMA')

Today I finally tried the fabled Ecstasy because I had to eventually discover what it was all about, 20 years after I first came upon it. The mushrooms last week were so beneficent and yet powerful that I felt it was finally time to conquer and understand the E experience as part of figuring out the different actions of serotonin entheogens and entactogens. And it was a lovely experience too and highly intriguing although its not a transcendental molecule, but rather a sensual and sensitive molecule, to be more precise an entactogen - that is it makes the ones you love seem even more tactile, cuddly and nice to be with, bonded and trusting, through the oxytocin it facilitates, at the same time as an exhilarated feeling of visual brightness and alertness. As the effects came fully on, the strength was almost too much. My eyeballs seemed to be shaking and I literally felt awash with serotonin as if I was standing in a shower. The garden seemed to be bulging out at me with an odd brightness that I could tell could be awesome in a dance hall setting. I found myself clenching my teeth tightly almost to the point of forcing them into my gums, but the sensation felt good and right - a form of keen concentration.

This was definitely a strong 'high' but clear of the mental confusion that can happen with full blown psychedelics, so one can carry on a conversation and engage a social process with heightened empathy and compassionate appreciation of others. Rather than stare at the ceiling and become lost in a psychedelic trance, I wanted to sit closer to my bemused partner, who seemed to have become feathery, as if both she and I had tingles running down our spines and over our skin. Its not that I had fallen madly in love but just had the insane sensual urge to crawl into bed and hug one another. And I felt very positively disposed, warm, relaxed and positive, in a mood with a lot of reserve and no paranoia, able to engage and enjoy social situations. And I felt exhilarated, energized and insanely clear, struck by the fact that this agent has a very good social affect, which can really bring people out of themselves so they bond as friends, or lovers in a vastly superior way to alcohol, which is why people at rave parties loved it until it got hunted down. I have to ask myself "Why was this banned?" "Why was no real assessment made of its capacity to induce far better social climates of tolerance and empathy than alcohol?"

I do have a concern about the risks of neurotoxicity, even if they are less than earlier studies reported, just because this drug is dumping heaps of serotonin and reversing the transporters as well, which is a fairly massive intervention. To avoid the Tuesday blues I take 5-hydroxy-tryptophan supplements over the ensuing 24 hours and have no ill after effects, except for being a little closer to tearfulness, but no worse than a night on psychedelics with too little sleep.

25C-NBOMe a Selective 5HT2a Psychedelic, with Synthetic Cannabinoids

Today I experimented with a super-potent psychedelic developed to significantly activate only the one kind of brain receptor 5HT2a believed to be involved in the entheogenic state and no others that can cause anxiety, or dreaminess, or shatter the thought process. The active dose to smoke is 150-300 micrograms, an amount as small as a grain of salt you can barely see, let alone measure, but the effects can be overwhelming. I took two very small inhalations of

the smoke and could probably have 50% more, but needed to measure the effect carefully. And yes it is fully entheogenic - both very powerful and ever so delicate! It begins with a pronounced serotogenic ‘high’ almost immediately but the full effects take a few minutes to settle in. Initially it seems to effect higher visual areas without as pronounced geometrical features as psilocybin, but that impression is deceptive. I had also had some cannabinoids and by the time the two were activated, I found I was falling into a rich kaleidoscopic sea of visions and entering the familiar eeriness of the entheogenic visionary trance. It has a very nice pure feeling, not only pure as a super-potent molecule, but also pure because its action is selective for the 2a receptor, confirming that this is the site of the entheogenic process, and evoking an experience free of the other potentially anxious effects of 2c and the loss of vigilance due to 1a.

Imagine looking at a still pool in the moonlight and something changes, so that, when a little breeze blows on the pool, causing ripples in the moonlight, instead of them dying away, as we look at them and pay curious attention, our hair stands a little on end as they respond as to a resonance and become brighter and clearer, and begin to come ever more alive, but this isn't just a pool 'out there' - it is one's entire conscious psyche 'in here' AND 'out there', one's vision, audition, tactile sensation, emotional feelings, the space between us and the space in and beyond the room, looking down deep down into the abyss, the tingles that run down one's spine, the musical spectra of the fat sizzling in the pan, the meaning behind the meaning behind - the whole experiential universe, be it dream, or reality, resonating uncannily as it becomes one with the conscious void filled with unfolding patterns and memories and dreams of memories and memories of dreams, all now resonating with the one that is all of our minds together experiencing the universe unfolding. Then, just as the void is alive and shining and at the same time empty in its peacefulness, as one's breathing comes to a standstill, the still point of the turning world, the dew drops into the shining sea and we slip back into the room around us, realizing yet again that we have made the unspeakable connection to the mystery that lies at the foundation of all conscious life, as we move in space-time towards our realization, and all of our destinations.

The synthetic cannabinoids are also a new experience. Very sharp and electric and easily reaching a level where one’s thought processes are running away to the point of mild anxiety, yet identifiably a cannabis type ‘stone’. The smoking involved with milligram quantities of relatively pure substance appears vastly less harmful than a tarry marijuana joint, although they are largely untested entities.

Entactogen (‘MDA’) plus Entheogen (25C-NBOMe) and Cannabis

On a second occasion I combined an entactogen, believed to be MDA, with a stronger dose of 25C-NBOMe. The entactogen taken in the early afternoon gave a clear, pleasant, sociable high, promoting a strong desire to converse intimately with my companions. Cannabinoids around 4pm gave the experience a wilder tinge on a walk over the nearby mountain. Toward evening, I inhaled an unspecified quantity of 25C-NBOMe and became launched into a paradoxical visionary state, in which the entactogen and entheogen combined to give a very positive emotional spin on the whole experience - wholesome as well as awesome! This is well known combination appreciated by LSD trippers in the 1960s. 25C-NBOMe is a deceptively strong, very pure psychedelic, which can move from appearing to be merely a glow on the surroundings one minute, to falling into a deep kaliedoscopic entheogenic trance the next. It has a very deep clear entheogenic effect when one falls into it. I class it as a very valuable research entheogen.

A problem emerged later in the evening, when my left eye began to have severely disrupted retinal vision with eerie haloes and vision loss unless I lay flat on my back, compounded by the psychedelic effect. I have had a similar effect transiently in the other eye on Viagra, probably due to vasodilation against the optic nerve, but the mix of serotonin releasers and agonists seemed to be exacerbating a vasoconstricting effect into a retinal migraine. I partially controlled this with a power walk back up the mountain, which was a scintillating experience of psychedelic lights. However the blurring didn't dissipate until next evening, in a throbbing red eyeball.

Now this turned out to be an indirect godsend. With this condition, anything that dilates your pupils can bring on an acute attack. A couple of months later when the conditon recurred on quiet evenings I had an eye check and found I had acute closed-angle glaucoma. I was promply sent to the accident emergency and given a laser operation on the spot to puncture a passage through each iris, which promptly relieved the condition. Had I not taken the psychedelics, I might have not had the condition fixed before I seriously lost my vision.

However one has to watch out carefully for peripheral vasoconstrictor effects in serotonin agents. Although 25C-NBOMe is strongly 5HT2A selective, 5HT2A receptors occur on both neurons and blood vessels. Closely related 25I-NBOMe has been associated with one acute hospitalization emergency in a susceptible individual, ostensibly at a carefully titrated dose - subject unresponsive, blue lips and systemic loss of ion balance (Elover).

Despite sleep and additional 5-hydroxytryptophan, next day I am somewhat brittle and hypoglycaemic. Day two I'm in fine form, but I have three observations about entactogens. Firstly, although they give a wealth of good feeling on the occasion and are very attractive as socially-bonding party drugs, they have higher costs than entheogens in the come down from excessive dumping of serotonin into the synaptic junctions and longer term reductions in transporter function. Secondly the drug wars are completely demented. It would be far better to legitimize MDMA and have people consuming certified pure entactogens than street drugs with a mix of more dangerous analogues and mimics, with possibly harmful impurities (see fig 20). Finally, serial dosing with entactogens and stimulants, combined with lack of sleep is a recipe for long-term functional depletion. The experience tends to make me gravitate back to natural entheogens, which have been safely consumed for millennia with minimal risk of harm, so here we go.

Maria Sabina consuming her sacred mushrooms.

Psilocybin again

A week later I checked out this performance against a second round of psilocybe mushrooms, which I have had a safe 36-year relationship with, after discovering a wonderful heritage movie of Maria Sabina doing a mushroom velada at Huautla de Jiminez (María Sabina: Mujer Espíritu http://www.youtube.com/watch?v=WEGeVUkrPRo). Of course again I fell into an entheogenic trance void amid the shrill sonic vibrations mushrooms are prone to, but the one advantage of the selective 5HT2A agonists is that they are a very clear mind state, free of the anxious thought rushes that can beset mushroom experiences. The reports of Aztec partakers fearing their heads were going to be crushed between two stones for being caught in adultery are not empty fantasies! On the other hand these disturbances can also be liberating when they bring to the surface and help resolve repressed conflicts and bring new realizations.

One needs to point out here that the entheogenic experience is deep, vast and complicated. We have up to four plausible processes, each potentially affecting the conscious state, 'kaleidoscopic' fractal waves of excitation travelling across the cortex, 'synesthesic' enhanced resonances between distinct cortical areas such as seeing and hearing, 'dream-like' changes to the Raphe nucleus and Locus coeruleus affecting arousal and reverie, and possible changes to thalmo-cortical feedbacks. It is one thing to see visual kaleidoscopes or experience visual-auditory synesthesia, but what is a fractal excitation of temporal episodic or semantic memory or parietal areas dealing with spatial relatioships and those dealing with complex scenes? What is synesthesia between our internal and external areas in the somatosensory and cingulate cortices going to do to our ideas of oneness with one-another and the universe? These complexities underlie the more subtle, far reaching, aspects of ego dissolution and the visionary condition.

Now let me get to the nub of this whole question of entheogens and the entheogenic experience. Human consciousness is caught between a rock and a hard place - the devil and the deep blue sea. This is the sentient aspect of the free-will dilemma - if we have no autonomous conscious will and are just the products of our brain dynamics, are the feelings we have of making personal conscious decisions delusory? No sane person wants to invest in this assumption. The sentient version is just as appalling. If subjective consciousness is just an internal model of reality constructed by the brain for our animal survival, all our personal experiences of the world are nothing more than a mirage, and we are caught in this infernal bottle, born alone to die alone, with no hope of a life hereafter, despite the subjective delusions of love and togetherness, in what is essentially a schizophrenic, existentialist nightmare, despite all our attempts to make meaning of the world. Yes I know we can make a claim that this is the evolutionary condition and that our neurotransmitters are giving us the feeling of togetherness, reinforced by our mirror neurons, still this is the stuff of a psychotic nightmare and why some people go to pieces faced with the enormity of psychedelic reality. The other option is that there is more to it. The second, saner option also has profound implications - that subjective consciousness, despite being a product of our fragile brains, is somehow a real phenomenon which possibly has influence on our physical circumstances, not just an internal 'epiphenomenal shadow', and our subjective experiences of reality, from birth to death, are somehow complementary to our physical presence in the natural world. It is this second option that is also the motivating raison d'etre for all our 'spiritual' and religious traditions. What the entheogens provide is a disembodied abstract form of existential consciousness, which is transiently freed from the boundaries imposed by the organismic framework of survival, so that it can come to terms of understanding of its own condition.

This is not something which can necessarily be seen objectively or retrieved and classified, as an external structure can be, but is a participatory form of abstract consciousness, which can take a variety of forms, just as the dreaming state, as a palpable sensory reality on a similar existential footing to waking reality, can adopt almost any kind of situation imaginable, but in the psychedelic condition, unlike the projected realities of dreaming, consciousness can adopt altogether different, more abstract forms, from spaitial kaleidoscopic structures, through visions of scenes, to a deep intimate sense of 'spiritual' integration and meeting with the essential conscious forces shaping the experiential condition. When I enter the entheogenic void I experience a return to this source condition, not as just an emotional feeling but as a veridical self-validating sensory experience, just as dreaming is not just imagination, but an inner sensory reality. It conveys to me a return of my consciousness to its unconstrained natural state, reflreshing my life journey by a return to its source condition. A condition from which the meaning and direction of my life takes form.

Complementary to this is the whole question we have investigated in detail in this article, about how each of the psychotropic substances affect brain dynamics through their receptor and transporter activities, and both by discovering how they act experimentally, and through their subjective experiences bringing us to a closer and more decisive understanding of how the conscious brain performs its elegant and complex tasks of cognitive and sensory processing, along with memory formation and anticipation of future situations. Thus discovering experimentally how the glutamate connection may facilitate both psychedelic and dissociative brain changes in rapidly fluctuating

activation dynamics provides a compelementary insight to the deep subjective commonalities of peak experience, despite the profound differences of action of these two types of agent.

The psychedelic experience is often described as a ‘trip’ because these experiences of falling into the cosmic condition can happen in the midst of the other things we are doing, as we lie beck for a moment or two in reverie and find we have entered this enchanted realm. Sometimes it may feel a little demented and we might again ask, “Is this redemption or a lonely dysphoric nightmare?” but as the experience progresses, one realizes one has made some kind of intimate contact with the utimate ground of sentient being, and when one comes back down from this tangled journey and pieces together the experiences, one often genuinely feels one has had an encounter with the ineffable source of existence. It is this entangled journey that lies at the heart of the rejuvenating and fulfilling experiences reported in the ‘genuine spiritual type’ experiences reported by Griffiths et al and ironically originally by Leary et al, in the Marsh Chapel experiments that triggered the psychedelic fall from grace. And it is here that the importance of accepting the central role of entheogens in our discovering our own inner identities, for entheogens present the best route we have to understanding the abstract fundamentals of consciousness, just as the LHC, as chaotic fundamental particle billiards, does for the foundations of physical cosmology.

Let me explain why. Psychedelics, and the dissociatives, induce profound changes in how the conscious envelope of subjective experience is generated, in a manner which induces phenomena extra-ordinary to waking and even dreaming reality, from deep fractal kaleidoscopic image spaces, through complex visionary sequences, to primal experiences of cosmic union. Many of these features share parallels with the sensitive dependence on boundary conditions possessed by chaotic systems and with edge of chaos complexity. The fact that they occur in an abstract form and present archetypal features, suggests the subject’s brain is being thrown into a state of internal chaotic resonance with its own internal dynamics, which may reflect deeper underlying principles of how subjective consciousness is generated, giving them a fundamental complementarity to dreaming experience and waking life. In so doing, they may bring us closer to understanding the essential nature of subjective consciousness than any other avenue, although this may be a dynamic participatory experience whose features cannot be fully described externally, requiring first-hand experience to fully fathom, consistent with the essentially first-person nature of subjective experience and in contrast to the second and third person accounts of religious doctrines and beliefs.

In this they may even hold a key to the way the brain uses the physics of quantum entanglement to anticipate events in real time and thus lead to a new deeper understanding of cause and effect central to our idea of free will and the existential dilemma. Animals possess subjective consciousnes not to compute probabilities alone but to anticipate immanent threats to survival and avoid them. Probabilities are insufficient to solve this because the lion can be on any path about to strike. The conscious brain uses wave function processing with many features in common with the wave-particle complementarity of quantum physics. Psychedelics may thus take us into an undiscovered realm of spooky space-time interactions which science is only beginning to uncover. Thus some aspects of shamanic thinking may be an intuitive investigation into founding cosmological principles.

Because psychedelics appear to operate through a second 5HT2a pathway, rather than disrupting all serotonin signaling pathways, they can achieve their powerful effects without grossly disrupting cognitive and memory processes in the way that delirants and to a lesser extent dissociatives do, so they have the greatest potential for investigation and discovery of the generative nature of consciousness. Science has hardly begun to have a model for extending subjective consciousness to the cosmological condition, and current descriptions, such as the Buddhist Bardo, or Vishnu dreaming cosmic reality tend to stem entirely from religious traditions. Our investment in intentional autonomy and the belief that our subjective conscious intentions can alter world futures extends to a description in which the universe at large also possesses subjective intentionality, which has profound implications for world futures in a situation where current attitudes are in a vacuum of schizophrenic views between apocalyptic religion and materialistic tragedy of the commons. Entheogens may hold a key to a description of universal consciousness consistent with the long-term future of our planetary survival, in replenishing the Earth, in the closing circle of the biosphere, rather than the scorched-Earth divisiveness of competing moral-apocalyptic theologies.

To ban psychedelics for half a century under penalties of long incarceration has been the most damning indictment of the shallowness of our culture and exposes the innate fear of the powers that be, controlling capitalist society, that the discovery of these internal realities might seriously unravel both our contrived religious traditions and our materialist consumer society in one fell swoop. But in turn, if they do provide a key to the nature of subjective experience, they could hold an oracle to the foundations of life, the universe and everything. This is the key existential question we all face in the mortal condition. Again this is not just a ‘spiritual’ question, although it has religious dimensions, but is a fundamental ‘cosmological’ question about how the conscious universe manifests itself and ourselves in space-time.

Ketamine

To take ketamine I insufflated powdered crystals from therapeutic sources. The effects are very peculiar to say the least. About three minutes later I have become aware that my consciousness is becoming vastly deranged. It's a feeling I can recognize because I have also experienced pure salvinorin-A, which has a similar dissociative effects. This can be very disconcerting, because your normal relation with your body and the world around you can take on very strange manifestations, where you literally become part of the surroundings, not just a fly on the wall, but you ARE the wall. You may feel you have turned inside out. It sounds ridiculous, but its evidentially true! And everything

you look at, and everything if you close your eyes, is wildly disassociated into alien kinds of conscious structure, in wild motion, as if your internal model of reality has come loose and is resynthesizing on different principles

For the first few minutes, maybe five or six, I'm trying not to swallow, and spit out occasionally, because, if it gets down the back of your throat, it can make you quite nauseous. Then I realize my nose feels cool and I am entering a state of peace. The anesthetic effect is taking me deep into a psychedelic reverie through pranayamic breathing. I fall deeper into the dissociated state and I realize that coming backwards through it all is an ever so overwhelming complete entheogenic experience similar in kind and feel to the classic psychedelics of simply awesome depth. A depth so inscrutable, you are touched by it, swept into silent awestruck oblivion - but still conscious - still there - still aware - somewhere in the aether, as the void breathes its delicate structured emptiness.

At some point, my partner knocks and opens the door to make sure I am okay. All I can say barely through the ice of immobility is that it is like the divining salvia 10,000 times over. I continue to witness drifting in and out of the entheogenic trance and note that this is a definite confirmation that, although the initial experience seemed more like salvinorin dissociation, the state is also able to manifest something intimately recognizable as a deep serotonin-like psychedlic reverie, confirming in my mind the deep association between the classic psychedelics and dissociatives, hinted at in the 5HT2a, MGluR2 and NMDA interactions discussed in the article. I begin to become curious what ketamine would be like taken along with a classic psychedelic. But then I realize that it would be impossible because my hands and feet are like clay tablets, or I have been set in quick drying cement.

I continue to recognize the depth and mystery of what I am witnessing. But then things take a more sinister turn. My mind is becoming memory-less. It's as if all my brain and memory circuits are reprogramming themselves and all the needles are beginning to point every which way. I know it's going to be alright, but it sure feels as if I am going to be stark staring mad forever. So I decide just to ride with the experience, because I will probably be able to remember it all when things settle down at the end of an hour or so. And I'm thinking about my hippocampus because I know what it does to your memory centers, and then suddenly its as if the dials have connected to the master index of all my life experiences, and here they are flashing before my eyes, just as they say about someone who is drowning, and near death experiences, but its not just my life experiences, but the very peak experiences, like the chain of the Himalayas.

I am suddenly looking right into the peak experience I had on ayahuasca, the Vine of the Soul, in Amazonian Peru in 1980, and all the other times I have been outside the inside out, as if every moment were written on a stack of cards and now they were flashing past in a flying shuffle. I realize I am looking back down on them in the same way Moses might look down on his life and the life of everyone from the mountain top, and that all the experiences of my life are coming into one cosmic focus of meaning and destiny. At this point I suddenly realize that everything I have ever done and everything I will ever do has been brought to this very moment and this very experience, and it is 'God', and my destiny coming to its true destination at this point, which is beyond time and space, coming from the very beginning, and for ever. I have this overpowering feeling of having been taken so far it is the full age of the universe and I have so far to get back to the land of the living. It is the same thing I have read about in near-death experiences where one's life flashes before one's eyes and one feels one is uniting with the universal self and could go with it or return to the incarnate world of individuals. But at the same time it is the universal mind coming to know and understand itself. At that point it seemed almost as if my life was now over. I had made the connection which gave my life its central meaning and though I might in future do nothing else and maybe I would never be able to come to this point again, my life had meaning in giving ultimate meaning to the totality witnessing and knowing itself.

If I look out at the room I still feel deranged, although feeling a little flatter though still depersonalized, or derealized is probably the better term. And then things come a little more into focus, and I realize I'm coming out and suddenly I am hit with the unbearable lightness of being, a ridiculous case of laughing gas splitting my sides, because of course nitrous oxide is a milder anesthetic of the same basic NMDA antagonist class, and I am simply hilarious that its all going to be okay again! And I look at the clock and its only an hour later, and so I lie there trying to soak up the experience, completely awe struck at the inscrutable point of no return, in becoming one with the eye of the universe coming to meet its destiny in knowing, as I am knowing and by the enormous journey I have taken. And so I try to express to my partner what it was like, but words still won't come and all I can do is utter complete existential overcharge in a fulminating cry "Aaaahhh!!!" And I stagger out into the living room with feet like snow boots, the outside world through the windows still looking like a dream, while I try to piece together the experience and whether it is all going to be lost in the oblivion of the sleep of forgetfulness.

How do you express these experiences? What do they all mean? Was this God? Was this a complete delusion? What is the final answer? Would you ever have a better chance on the edge of life and death? Or is the living brain the crucible of existence and the one chalice of the infinite through which the universe can pass? And what of the effects and consequences? Ketamine is a strong anaesthetic and I worry about the cumulative effects on memory of repeated use of a drug which both has very strong effects on neuronal excitability and manifest effects on the memory process, which is something we have at best limited conscious control over, so it is definitely something I wouldn't consider taking often. The strange sensations I had about my memory during the experience is enough to convince me of this, although afterwards I have been able to recall as much of the experience as in any other entheogenic experience, and cannabinoids can also disrupt short-term memory.

Salvinorin-A

When taken directly from the leaves of *Salvia divinorum*, salvinorin has a mildly disturbing effect on both consciousness and memory which is different from the classic psychedelics in that it appears to involve crumpled surfaces rather than kaleidoscopic geometries and has an odd effect on memory as if one feels that one's memory has always been submerged in this condition when one knows this is not true. The two times I have taken pure salvinorin, around 0.7-1 mg vaporized, the effects have been totally dissociative and completely overpowering, with my body image completely unraveled. The first time I felt I was in an enormous aircraft hangar with a gigantic wheel rolling over my body flattened and rolled out like a sheet of paint. The second time I fell to the floor as my body turned inside out and broke into the flagellating surfaces breaking up the space of the room around me. By the time I have realized I can handle the experience it is already beginning to fade. Yes these experiences are profound but they are also transient and leave little time to come to terms with them contemplatively and they do have strong undertones of dysphoria, although fascinating and challenging. So I don't class them as entheogens but as hallucinogenic dissociatives.

Return to Forever: An Heroic Dose

Today a little over six months after the psychedelic episodes just before my emergency laser eye surgery as a proof of principle for the cure, I set out to have a heroic dose of sacred mushrooms to test the water after months of parched ground, leaving me drifting in mid life crisis. The little sprout fruiting buds I consumed were severely hyper-potentiated. What could have become a mushroom with a cap 10 cms across only gets to be the size of a pea, but with all the active ingredient of the never-to-become giant cap caught in its base, so 1.5 gms of this crispy dried stuff can be a dose of epic proportions. Coming out the helter-skelter tunnel of an overwhelming mushroom experience - what do I make of the role of entheogens? Are they beneficent world-healing allies? Are they here to heal the biosphere and show us the secret of the existential quest?

As previously noted, the experience comes on with a symphony of shrilling vibrations that, as they overtake me, spiral me into the visions. I love this herald of the onslaught of sacred mushrooms dearly. It is for me a synesthesia which is sensitive to my mental awareness, a tunable whiplash that takes it far beyond a drug effect into the continuum of shamanistic non-ordinary reality. Visions come and go of impossible experiences I know I have had and witnessed first-hand yet know I could never have happened.

"And you also see our past and our future, which are there together as a single thing already achieved, already happened . . . I saw stolen horses and buried cities, the existence of which was unknown, and they are going to be brought to light." Maria Sabina

At the peak I felt as if I was suspended in a state of light-induced electrocution. It was searingly high and at the same time utterly pure. If I were on any form of synthetic I would be on the verge calling for an ambulance. It's only because it is a natural agent of the highest, purest quality that one can do something so extreme. And this makes it a living path, a living sacrament. I could barely get up from the bed and walk down the hall. As I sat breathless in the living room, non-ordnary reality was bursting out of my sub-conscious and across my peripheral vision so I was simultaneously in about five places at once. I was overwhelmed but at the same time didn't feel poisoned, just physically illuminated - animated to the point of annihilation. Idyllically my eyes didn't throw any of the previous acute primary angle closure crises from my previous case studies before my laser operation, even though I could barely read because my pupils were so dilated.

My whole creative life has been defined and fertilized by sacred mushrooms. All my scientific research, all my shamanic and messianic journeys, many of my love affairs and all of my spiritual quest. I consider myself a direct protege of Maria Sabina and hold true to the path of the teonanactl shaman - which my whole life journey is an expression of. If this wasn't a first schedule toxin I would have spent my entire life teaching all and sundry the path of the living sacrament of the Tree of Life true to my name and destiny. So you are right! ... how can I pretend that the sacred mushroom of immortality doesn't have a pivotal role in unfolding the healing of humanity?

That said, we need to be very cautious. My anxieties about the misuse of ultimately potent visionary agents is very real. Maria Sabina herself has done some mortifying things leading to a young person dying of fear and the ayahuasceros and yopo snuffers have plotted curses against their enemies for witchcraft and resorted to poisoning their victims. All the societies that have used entheogens have in various extreme ways abused them too, setting up fearful shamanic visions of conflict, violence and mortality. So these allies and agents do have the power to heal the planet, but only in the hands of enlightened people who are selfless and devoid of delusions and pretenses. We need to be guides if we can muster the strength of character and non-violence to show people the way of unfolding. How can a person who claims to be a/the messiah of the Tree of Life not have delusions of grandeur? Because the mushroom speaks, I have no need of pretenses or any form of grandeur. Mushrooms made me realize my calling as Christo Rey twenty years before the millennium on a wild moonlit night in the wilderness. They took me to the Holy Land, where instead of being shut away in the Jerusalem syndrome psych ward, I was welcomed by liberal Jewish people as a kindred spirit and given the spiritual keys to the city.

I have taken and immensely enjoyed the intensity of ayahuasca, despite its nauseating dimensions, but for me sacred mushrooms provide the kindest, most organically acceptable face of the entheogenic abyss. They aren't quite as colourful as ayahuasca but the depths of the non-ordinary reality is as inscrutably potent and sufficient to bring one to

terms with the ultimate incarnations of the bundle of life, death, the hereafter and the primordial beginning, alpha to omega. As the recent psychedelics conference in Oakland laments, the greatest tragic injustice of the entire Western tradition is the tabooing of entheogens by mainstream society under pain of inquisitional repression. This applies acutely to the repression of the sacred mushroom.

Mushrooms have given me extraordinary and horrific visions whose significance I still ponder to this day. Far from the Chilean ayahuasca messiah who burned his own baby alive because he thought it was the antichrist, I have nurtured all my children faithfully in the sacred way. I had a horrific vision that my firstborn daughter would be doomed to an obstruction to her own fertility as some sort of hideous sacrifice to my own destiny. Then her first offspring had Downs syndrome. What am I supposed to make of this? Is it sheer coincidence? Is it destiny? Is what happened somehow a consequence of having that deluded vision? Was it a prophecy, or was it a curse? What is the relationship between prescience and history? These are the difficult questions shamans have to learn to ponder, often with no answer but continuing participation in this magical world, so long as we both shall live.

So, as the effects begin to stabilize, I look up at Maria Sabina's image, which always sits as a shrine on our mantle altar, and ponder the karmic connection I have with sacred mushrooms, with world destiny and with the healing of the planetary future and reflowering of sexual reunion of the generations of humanity, and of all life. Without sacred mushrooms I would be a nobody reading about mysticism and wondering what the mystery was. With sacred mushrooms, my life unfolds before me as a great journey, tacking my way up an endless fjord, with veladas marking the major tipping points where the journey of meaning turns about and we all duck for cover as the mainsail boom swings over our heads, amid strange affirmations from the world around us that this is not just an dream-like fantasy but the unfolding living universe to which we have become inordinate sensitives.

Because I partook mid afternoon, by mid to late evening the effects had returned to a mild high and I could sleep a reasonable night. Next morning I am fresh and clear in the sparkling sunshine. A new man in a world reborn with the youthful freshness of a new day, my creativity and sense of emergence rekindled.

"But I, I am lord of two ways. I am master of up and down. I am as a man who is a new man, with new limbs and life, and the light of the Morning Star in his eyes."¬†
D H Laurence The Plumed Serpent

Is it my karma to tell the world that sacred mushrooms are the living sacrament of the Tree of Life, consummating the destiny of the living planet? That Christianity is merely a shadow - a sacrificial husk of a sacramental tradition lacking its sang-raal, instead living the sacrificial filicide of a God killing his only begotten Son to provide the empty sacrament of soma and sangre - bread and wine so that, instead of discovering the gates of immortality ourselves, we must believe in Him in the delusion that such violence of consuming the flesh and blood of the dead god will provide eternal life. At best one can say all the traditional religions in their delusion were pointing prophetically to this realization, so that Christianity as our immediate forebear in the sacramental tradition is in a sense a forerunner of the unveiling of the holy grail.

The tragedy here as I see it is that sacred mushrooms are the most beneficent of the natural visionary sacraments but their tradition has been stifled by the DEA ad the war on drugs. Ayahuasca was never able to be conquered in the same way, because the Amazon is a law unto itself and the traditions of ayahuasca use have stayed strong in tribal traditions, amid resurgences of endemic worship like Santo Daime and the UDV. What is key to the unfolding is showing the world that sacred mushrooms are the holy communion which doesn't make one puke and actually feels pure and clean, so it could really become incorporated into the very fabric of an advanced enlightened society and become its raison d'etre without being a hard road to hoe.

So do I have a karmic connection here or what? Of course I am just one of a host of people who have taken sacred mushrooms and one of many enlightened people who try in their art, in their music, in their scientific research, or social projects, from remission of terminal angst, to inducing genuine spiritual experience among middle aged straight subjects, try to pave the way for an new world order of visionary emancipation. But the karmic connection remains. Who else stands alongside me as the Cristo Rey of the sacred mushroom in this way? Who else can show the way to bring the whole tortured tide of history, belief and delusion to its natural consummation? We know life is a free naked lunch, but how do we give back the flood tide of abundance while we still walk on this magical Earth?

Dreaming

I have had many strange dreams in my life, some apparently precognitive and some manifestly lucid. In one, I looked at my hands and found my consciousness split in three, one self was lucid, but lost in the dream universe, I walked up to a woman, and stared down deep into her eyes desperately asking how I could ever find the way back to the Ixtlan of the real world, but she just shook her head smiling as a blast of spray hit my body on the promenade, one self was shooting upwards ever faster, and the third was bumping on the ceiling of my bedroom, reassuringly witnessing my body asleep in the bed below. In another formative expereince, I had two consecutive nightmares that I was being

stung. My wife awoke before me to feed our infant daughter and I went back to sleep after telling her of the nightmare. An hour later I was stung wide awake by a wasp which had crawled under the covers after my wife opened the bedroom window. This opened my eyes to the implications of precognitive dreaming. But here I relate a time-spanning dream during this entheogenic discovery process.

I dreamed I was at a place like a school and someone had been shooting at some other people and there were little silver bullets on the ground. Then later I realized I had to leave and worried that I would become a target myself. As I was walking anxiously down a drive through the site I realized there was a right turn just before the end which went down an alley lined by an avenue of trees, so it was hard for the shooter to get a line on me. I managed to slip anxiously away and then managed to take off on my motor cycle around the block, where I ran into a very crowded situation trying to push the heavy bike up hill. I then found myself on a crowded truck but at the same time thought I was in a physics lab and wondered why I had spent so much time in the lab session and had had few or no lectures. The episodes with the shiny bullets and the physics lab have strong echoes in two television programs we were watching the night before, Castle about a murder in which the bullets were crucial evidence, and The Big Bang Theory, which is about nerdy physics graduates. However there are two features of the dream, the right turn down the alley and pushing my bike up a hill, which appear as a lock and key to future events that happened after the dream. The next day, I was fixing a lock on one of our French doors and suddenly remembered I had thought of looking for a locksmith's supplies I had visited a few years before in case the lock was cheaper there. It was long enough ago that I had to look up the name and address on the internet, but when I rode out around the block on my push bike the destination was down a cull de sac on the right just before the end of a short side street and when I arrived at the place, I found that I had to push my bike up a steep slope and couldn't ride it to get out again. Thus two incidental components of the dream, neither of which related to my immediate past, were combined in a form which together point to an experience I was going to have after the dream, reflecting the double blind study in "An Experiment with Time" (Dunne). Since the role of subjective consciousness in evolution appears to be critically to anticipate threats to survival, in situations where computational processes become intractable and such choices may also depend on contingencies which have yet to arise in future, further exploration of the anticipatory capacity of waking, dreaming and entheogenic experience is an urgent priority for our understanding of life and consciousness.

Before the alkaloid in *Banisteriopsis caapi* was found to be harmine, (along with related tetrahydro-harmine and harmaline), it was initially named 'telepathine' because of reports about ayahuasca's telepathic powers, in association between harmine as MAO inhibitor and the DMT from *Psychotria viridis* in the brew. Maria Sabina's description of her mushroom experiences also contain references to thier 'prophetic' propensities and one study (Millay) claims success above random levels with remote viewing on psilocybin. Without succumbing to the naïve claims made by some psychedelic writers, we need to keep an open mind about exploring the space-time properties of the entheogenic experience. Because it allows the brain to witness its own inner dynamics consciously in a way which is responsive to our attention it is effectively the mental equivalent of a cloud or bubble chamber, a unique facility for fundamental research we cannot afford to suppress, given the conscious mind being both the central arena through which all our life and action passes and the deepest enigma facing the scientific description of reality.

Scopolamine and Hyoscyamine

Oliver Sacks (2012) recounts the following experience with Artane – a muscarinic antagonist like scopolamine illustrating why I am reluctant to take this class of drug:

One Sunday morning I counted out twenty pills, swallowed them with a mouthful of water, and sat down to await the effect. Would the world be transformed, newborn, as Huxley described in "The Doors of Perception," and as I myself had experienced with mescaline and LSD? … I had a dry mouth and large pupils, and found it difficult to read, but that was all. There were no psychic effects whatever - most disappointing. I did not know exactly what I expected, but I expected something. I was in the kitchen, putting on a kettle for tea, when I heard a knocking at my front door. It was my friends Jim and Kathy; they often dropped round on a Sunday morning. "Come in, door's open," I called out, and as they settled themselves in the living room I asked, "How do you like your eggs?" Jim liked them sunny side up, he said. Kathy preferred them over easy. We chatted away while I sizzled their ham and eggs - there were low swinging doors between the kitchen and the living room, so we could hear each other easily. Then, five minutes later, I shouted, "Everything's ready," put their ham and eggs on a tray, walked into the living room - and found it empty. No Jim, no Kathy, no sign that they had ever been there. I was so staggered I almost dropped the tray. … I was not only shocked but rather frightened, too. With LSD and other drugs, I knew what was happening. The world would look different, feel different, there would be every characteristic of a special, extreme mode of experience. But my "conversation" with Jim and Kathy had no special quality; it was entirely commonplace, with nothing to mark it as a hallucination.

"Careful, Oliver," I said to myself. "Take yourself in hand. Don't let this happen again." Sunk in thought, I slowly ate my ham and eggs (Jim and Kathy's, too) and then decided to go down to the beach, where I would see the real Jim and Kathy and all my friends, and enjoy a swim and an idle afternoon. I was pondering all this when I became conscious of a whirring noise above me. It puzzled me for a moment, and then I realized that it was a helicopter preparing to descend, and that it contained my parents, who, wanting to make a surprise visit, had flown in from London and, arriving in Los Angeles, had chartered a helicopter to bring them to Topanga Canyon. I rushed into the bathroom, had a quick shower, and put on a clean shirt and pants - the most I could do in the three or four minutes before they arrived. The throb of the engine was almost deafeningly loud, so I knew that the helicopter must have landed on the

flat rock beside my house. I raced out, excitedly, to greet my parents - but the rock was empty, there was no helicopter in sight, and the huge pulsing noise of its engine was abruptly cut off. The silence and emptiness, the disappointment, reduced me to tears. I had been so joyful, and now there was nothing at all. I went back into the house and put on the kettle for another cup of tea, when my attention was caught by a spider on the kitchen wall. As I drew nearer to look at it, the spider called out, “Hello!” It did not seem at all strange to me that a spider should say hello (any more than it seemed strange to Alice when the White Rabbit spoke). I said, “Hello, yourself,” and with this we started a conversation, mostly on rather technical matters of analytic philosophy. Perhaps this direction was suggested by the spider’s opening comment: did I think that Bertrand Russell had exploded Frege’s paradox? Or perhaps it was its voice - pointed, incisive, and just like Russell’s voice, which I had heard on the radio.

Porta, a colleague of Galileo reported a "man would sometimes seem to be changed into a fish, and flinging about his arms would swim on the ground, another would believe himself turned into a goose and eat grass, beat the ground with his teeth and flap his wings". "My teeth were clenched, and a dizzy rage took possession of me. I knew that I trembled with horror, but also that I was permeated with a sense of well-being. My feet were growing lighter, expanding loose and breaking from my body. Each part of my body seemed to be going off on its own. At the same time I experienced an intoxicating sense of flying. The frightening certainty that my end was near through the dissolution was balanced by an animal joy in flight ... the clouds the lowering sky, herds of beasts, falling leaves quite unlike ordinary leaves, billowing streamers of steam and rivers of molten metal."" (Rudgeley 95). Johannes Nieder (1692) gives the following account: "having placed a large bowl on top of a stool, she stepped into it and sat herself down. Then rubbing ointment on herself to the accompaniment of magic incantations, she lay her head back and fell asleep. With the labour of the devil she dreamed of Mistress Venus and other superstitions so vividly that crying out with a shout and striking her hands about, she jarrd the bowl in which she was sitting and falling down from the stool seriously injured herself about the head. As she lay there awakened the priest cried out "Where are you? You are not with Diana ... you never left this bowl!" (Harner (ed) 131).

“The James-Town Weed (which resembles the Thorny Apple of Peru, and I take to be the plant so call'd) is supposed to be one of the greatest coolers in the world. This being an early plant, was gather'd very young for a boil'd salad, by some of the soldiers sent thither to quell the rebellion of Bacon (1676); and some of them ate plentifully of it, the effect of which was a very pleasant comedy, for they turned natural fools upon it for several days: one would blow up a feather in the air; another would dart straws at it with much fury; and another, stark naked, was sitting up in a corner like a monkey, grinning and making mows [grimaces] at them; a fourth would fondly kiss and paw his companions, and sneer in their faces with a countenance more antic than any in a Dutch droll. In this frantic condition they were confined, lest they should, in their folly, destroy themselves — though it was observed that all their actions were full of innocence and good nature. Indeed, they were not very cleanly; for they would have wallowed in their own excrements, if they had not been prevented. A thousand such simple tricks they played, and after eleven days returned themselves again, not remembering anything that had passed.” – The History and Present State of Virginia.

An overdose on butylscopolamine. “It felt so indescribably weird. It was as if nothing was real and I began to forget who I, and everybody around me, was. I remember looking at the ceiling and it started bubbling. I remember seeing some very real hallucinations and feeling intensely energized and happy. I blacked out - my brother’s friends found me in the woods, I was conscious upon their arrival but collapsed in mid-discussion, they brought me home. I remember a little about coming home, it was a familiar place, but a new type of magical presence was animating it. At this point I had forgotten I took the drug and I went to my room to sit on my couch (I don’t have a couch in my room). I remember lighting up cigarette after cigarette and having a great old time talking to random strangers at a very social and easy going party (I don’t smoke cigarettes, and the only people who came in my room that night were my parents and brother). They drove me down [to hospital] and apparently the whole way there I thought we were riding some type of laser train. When I got there I got really violent with the nurses so they strapped me to the bed and the first 24 hours after being admitted to intensive care I can’t remember at all, the next two days I remember vividly accompanied with memories of outrageous things like talking snakes calling me names (the serious delirium began to subside after about four days). I saw my baby sister sit up in her cradle and shoot lasers into the air, I got into a very heated argument with a cardboard smiley faced sun on the wall. At one point all my family was standing around me asking me who they were and all I knew was my father’s name (but I couldn't remember that he was my father). I didn’t remember anything at first but as time went on and my family told me stories some of it came back” (Erowid).

12: Why the Neurotransmitters: Cosmology and Evolution

This brings us back to a fundamental question. Why does the brain use these neurotransmitters in such characteristic ways to do with emotion, wakefulness and sleep, vigilance and reward? This takes us back all the way to the emergence of life and to the cosmological relationships defining the biomolecules, from ATP to RNA, and the various biological amino acids. The elementary neurotransmitter types, many of which are fundamental amino acids (glutamate, glycine, GABA) or amines derived from amino acids (serotonin, dopamine, histamine, choline) have primordial relationships with the membrane, as soluble molecules with complementary charge relationships with the hydrophilic ends of the phospholipids.

Tryptophan, the amino acid from which serotonin is generated, plays a key role in the transfer of electric charge in the earliest forms of photosynthesis. In *Rhodobacter sphaeroides*, there are 39 tryptophan residues surrounding the porphyrin center. Initiation of the electron transfer reaction by excitation results in a transient change in the absorbance at UVB, near the peak of the tryptophan absorbance band. To make serotonin from tryptophan, oxygen is needed, and in the earliest geological times the Earth's atmosphere had little oxygen. Thus, serotonin is made specifically in unicellular systems capable of photosynthesis and the cellular production of oxygen. Consequently serotonin is up to 100 times more plentiful in plants and animals have ceased to synthesize tryptophan depending on plants for their supply. This relationship with light continues to this day in human use of melatonin to define the circadian cycle and serotonin in wakefulness and sleep, with light deprivation causing depression through serotonin.

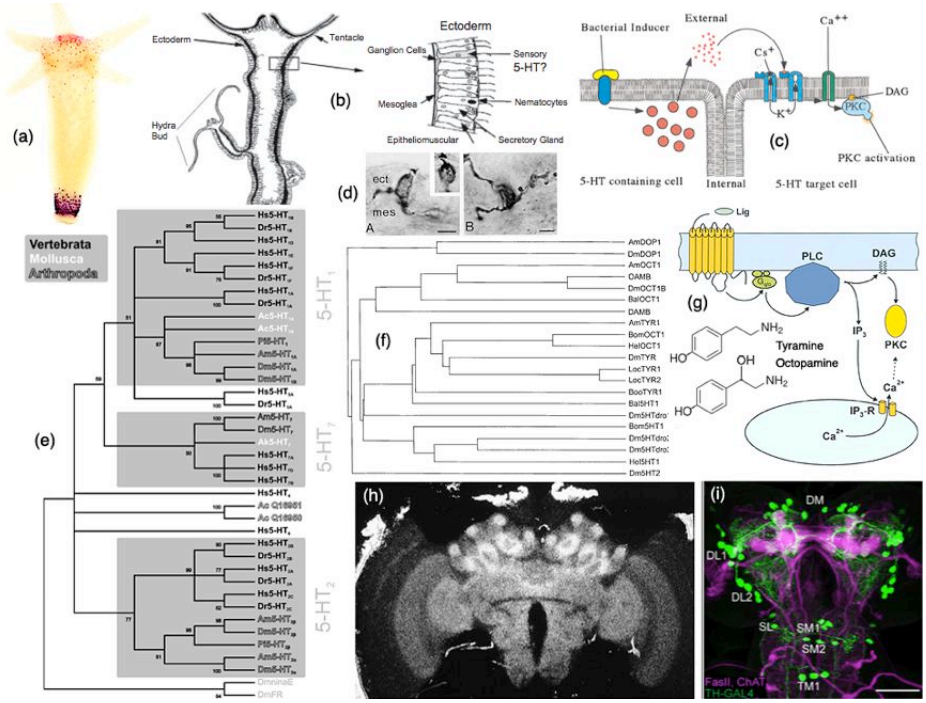


Fig 24: **(a)** Neuropeptides in hydra illustrate the diversity of neurotransmitters (Grimmelikhuijzen et al). **(b,c)** Model mechanism of serotonin signalling in coelenterates causing metamorphosis (McCauley et al) includes the diacylglycerol PKC pathway and **(d)** involves ectodermal neurons (Umbriaco et al). **(e)** Evolutionary diversification of 5HT1 and 5HT2 receptor families occurred before the diversification of molluscs, arthropods and vertebrates (Blenau & Thamm). **(f)** Evolutionary diversification of insect receptors showing serotonin, dopamine, taurine and octpamine (Blenau & Baumann). **(g)** Arthropod signalling uses the same pathways as in vertebrates (Blenau & Baumann). **(h)** Serotonin staining neurones in the honey bee, especially in mushroom bodies facilitating associative learning and olfaction (Blenau & Thamm). **(i)** Dopamine neurones (green) in the furit fly (Selcho et al).

From the gene diversity for serotonin receptors, the 5-HT1a receptor is estimated to have evolved 750 million to 1 billion years ago, before the muscarinic, dopaminergic and adrenergic receptor systems (Peroutka & Howell, Peroutka) and long before the Cambrian radiation defining multicellular animals. This places the emergence of receptor proteins and their neurotransmitters as occurring before the multicellular nervous systems as cell-to-cell signaling molecules essential for survival and positive and negative responses to nutrition and danger. The need for multimodal molecular messengers thus arises from the need for cells to have a variety of signaling molecules modulating key motivational and aversive aspects of survival strategy.

It also explains that neurotransmitters originated from direct signalling pathways between the cell membrane and gene expression in the nucleus of single cells, highlighting why changes in gene expression such as that of *egr*-2 in psychedelics may be central to psychedelic neurotransmitter action, rather than just flow-on excitation. It has also been suggested that key enzymes in neurotransmitter pathways may have become ubiquitous through horizontal gene transfer from bacteria (Iyer et al).

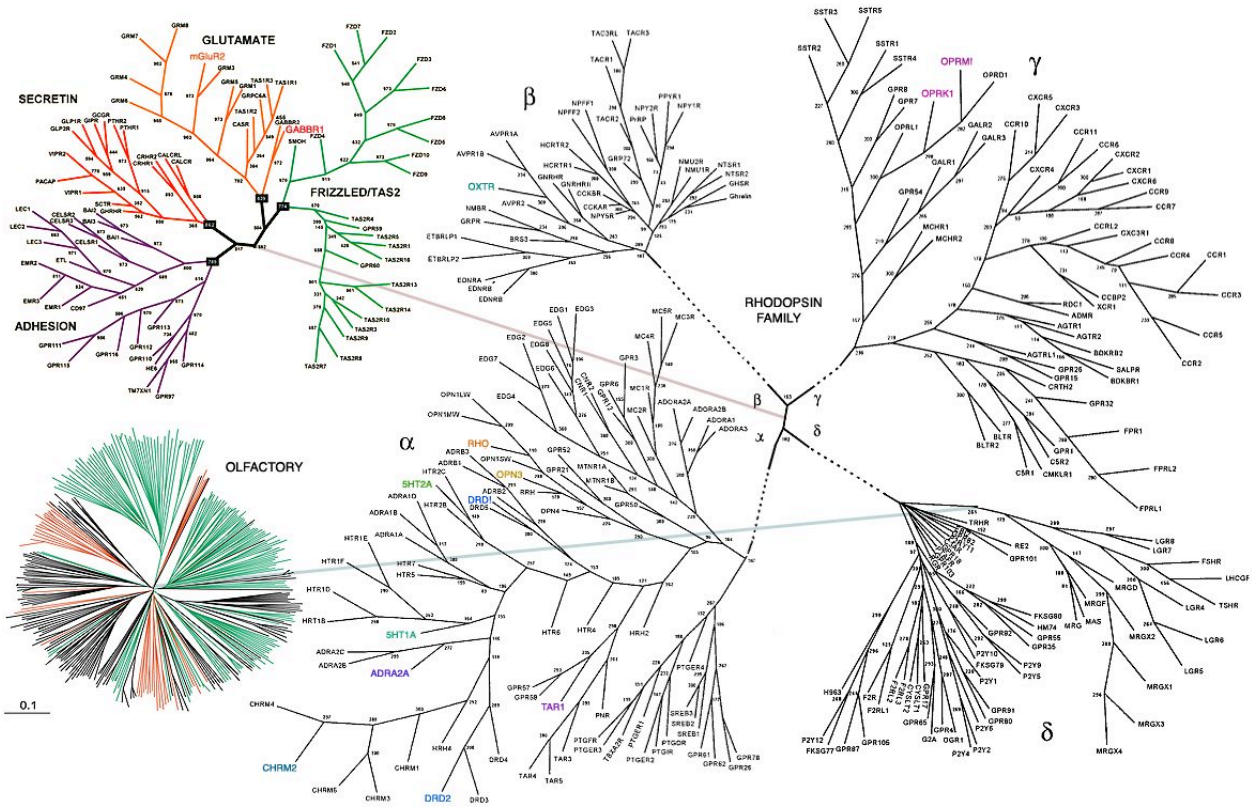


Fig 25: Evolutionary tree of the human G-protein linked receptors with examples highlighted in color. On the alpha branch are serotonin 5HT1A and 5HT2A, dopamine D1, and D2 (DRD1, DRD2), adrenergic α2a (ADRA2A), muscarinic acetylcholine (CHRM2), trace amine TAR1, as well as rhodopsin (RHO) and encephalopsin (OPM3). On the glutamate branch are metabotropic glutamate mGluR2 and GABA GABBR1. On the beta branch is oxytocin (OXTR) surrounded by vasopressin receptors and Ghrelin. On the gamma branch are opioid κ and μ (OPRK1, OPRM1). Olfactory and the non-rhodopsin receptors are linked to their respective points on the rhodopsin tree. (Fredriksson et al, Zozulya S. et al). Vertebrate olfaction also involves trace amine TARs, and rhodopsin-like and glutatmate-like vomeronasal receptors (Spehr & Munger). Insect olfaction uses both G-linked receptors and ionotropic receptors related to the NMDA receptor class (Abuin et al, Croset et al, Silbering et al). The 5HT receptors form evolutionary families in terms of the G-coupling types (Nichols & Nichols, Bockaert et al in Müller & Jacobs, Roth et al 2000). Gq/11-coupled 5HT receptor 2a, 2b, 2c activation leads to the hydrolysis of membrane phospho-inositides, resulting in the formation of diacyl-glycerol (DAG) and inositol phosphates, which then act as signaling molecules to activate, for example, protein kinase C (PKC) and elevate intracellular calcium, respectively. Gs-coupled 5HT receptor 4, 6, 7 activation leads to stimulation of adenylyl cyclases, resulting in the conversion of ATP to cyclic AMP (cAMP). Cyclic AMP is a ubiquitous intracellular messenger that interacts with numerous targets, including cyclic nucleotide-gated ion channels and the phosphorylating enzyme protein kinase A (PKA). Gi/o-coupled 5HT receptor 1a-f and 5a,b activation leads to inhibition of adenylyl cyclase and decreased production of cAMP as the primary functional end point. These receptors also form heterodimers both with one another e.g. 1a and 4 and with other receptors e.g. 2a and mGluR2. Dimerization can alter signaling pathway activation. Psychedelics are also believed to alter the G-protein expresso of the 2a receptor (fig 10). 5HT3 is an evolutionarily distinct ionotropic receptor.

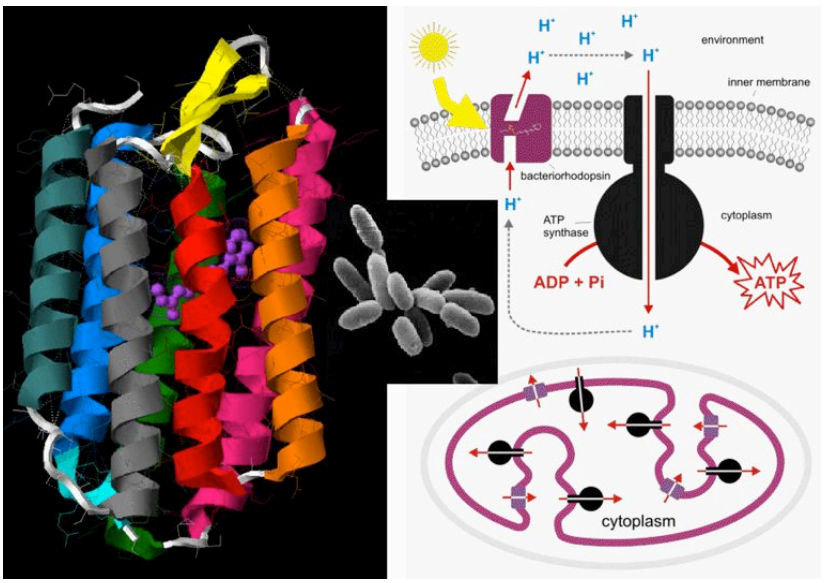


Fig 25b: The extremely ancient origin of the rhodopsin family of heptahelical receptors can be seen from the ultra-primitive archaeal photosynthesis in Halobacteria, which lacks any form of electron transport, relying on direct coupling between photo-stimulated chemiosmotic H^+ pumping and H^+ generated ATP formation, based on bacteriorhodopsin, which is heptahelical, uses retinal and shares distant sequence homology with vertebrate rhodopsin (Pardo et al, Taylor & Agarwal, Soppa, Ihara et al).

This ancient origin is confirmed by the fact that receptor proteins, second signaling pathways and key neurotransmitters are known occur widely in single-celled protists. Both *Crithidia* and *Tetrahymena* were demonstrated to contain norepinephrine, epinephrine, and serotonin (Blum 1969). The aggregation of slime molds such as *Dictyostelium* is mediated by cyclic-AMP and uses glutamate and GABA (Halloy et al, Goldbeter, Taniura et al, Anjard & Loomis). The ciliated protozoan *Tetrahymena pyriformis* (Brizzi & Blum, Essman) and flagellated *Crithidia fasciculata* (Janakidevi et al) utilize serotonin, and the former also metabolizes dopamine and epinephrine (Takeda & Sugiyama, Nomura et al). *Tetrahymena pyriformis* also has circadian light-related melatonin expression (Köhidai et al). *Trypanosoma cruzi* could be induced to differentiate by increased cAMP levels that resulted from addition of epinephrine (Gonzalez-Perdomo et al). Species of Entamoeba secrete serotonin and the neuropeptides neurotensis and substance P (McGowan et al) and release and respond to catecholamine compounds during differentiation from the trophozoite stage into the dormant or transmissible cyst stage (Eichinger et al) and Plasmodium falciparum malaria replication can be blocked by 5HT1a agonists (Locher et. al).

Consequently the major neuroreceptor classes have a very ancient origin, with the 5HT1 and 5HT2 families diverging before the molluscs, arthropods and vertebrates diverged, close to the level of the founding metazoa. Sponges, with only two cell types, express serotonin (Wayrer et al) and have been shown to have the critical gene networks to generate synapses, in a pre-coordinated form (Conaco et al). Coelenterates already have all the key components of serotonin pathways, involved in signaling by sensory cells and neurons, despite having only a primitive nerve network (McCauley et al, Umbriaco et al). Given this ancient origin serotonin is also found to play a key role in development and embryogenesis. In Molluscs, serotonin is involved in the determination of the animal pole during early blastula stages (Buznikov et al). [H^3]–5-HT binding is seen in the blastula and gastrula of sea urchins (Brown and Shaver). In mammals, the expression of serotonin receptors occurs at the earliest stages of ontogeny and is activated by circulating plasma serotonin from the mother. In the early stages of brain development, serotonergic neurons formed in the midbrain immediately sent out extensive fibers to the forebrain (Azmitia in Müller & Jacobs). In humans, 5-HT1a receptors are at their highest levels before birth (Bar-Peled et al).

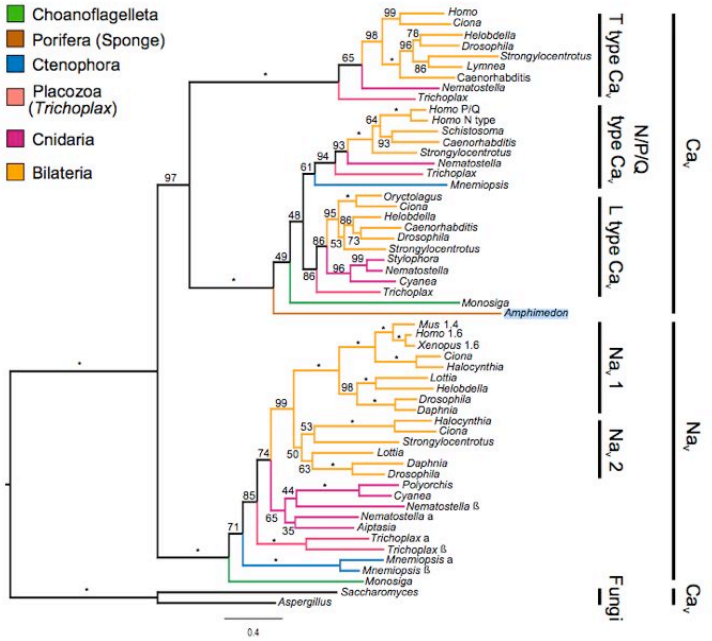


Fig 26: Evolutionary diversification of Na^+ channels from Ca^{++} channels, essential for the action potential, appears to have occurred before the existence of nervous systems in founding single-celled eucaryotes leading to the metazoa before the choanoflagelates such as monosiga (Liebeskind et al).

Thus we can see how the survival modalities of complex organisms have continued to be mediated by classes of neurotransmitters modulating key motivational, aversive and social dynamics with ascending central nervous system complexity. There are thus strong parallels in how the key classes of neurotransmitters modulate affect in organisms as diverse as arthropods and vertebrates.

Functional studies in the honey bee and fruit fly have shown that serotonergic signaling participates in various behaviors including aggression, sleep, circadian rhythms, responses to visual stimuli, and associative learning (Blenau & Thamm). Serotonin in lobsters regulates socially relevant behaviors such as dominance-type posture, offensive tail flicks, and escape responses (Kravitz, 2000, Sosa et al. 2004). 5-HT-regulated social and mental behaviors increased in number and complexity as these functions became more advanced and complicated. The reward system in insects uses octopamine, which is the presumed arthropod homolog of norepinephrine, rather than dopamine. In insects, dopamine acts instead as a punishment signal and is necessary to form aversive memories (Barron et al, Schwaerzel et al, Selcho et al). Experimental evidence suggests that in flies dopamine modulates locomotor activity, sexual function and the response to cocaine, nicotine, and alcohol (Hearn M et al). Octopamine regulates

desensitization of sensory inputs, arousal, initiation, and maintenance of various rhythmic behaviors and complex behaviors such as learning and memory, endocrine gland activity and induces mobilization of lipids and carbohydrates (Farooqui). Web building in spiders is likewise affected by stimulants and psychedelics (Dunn).

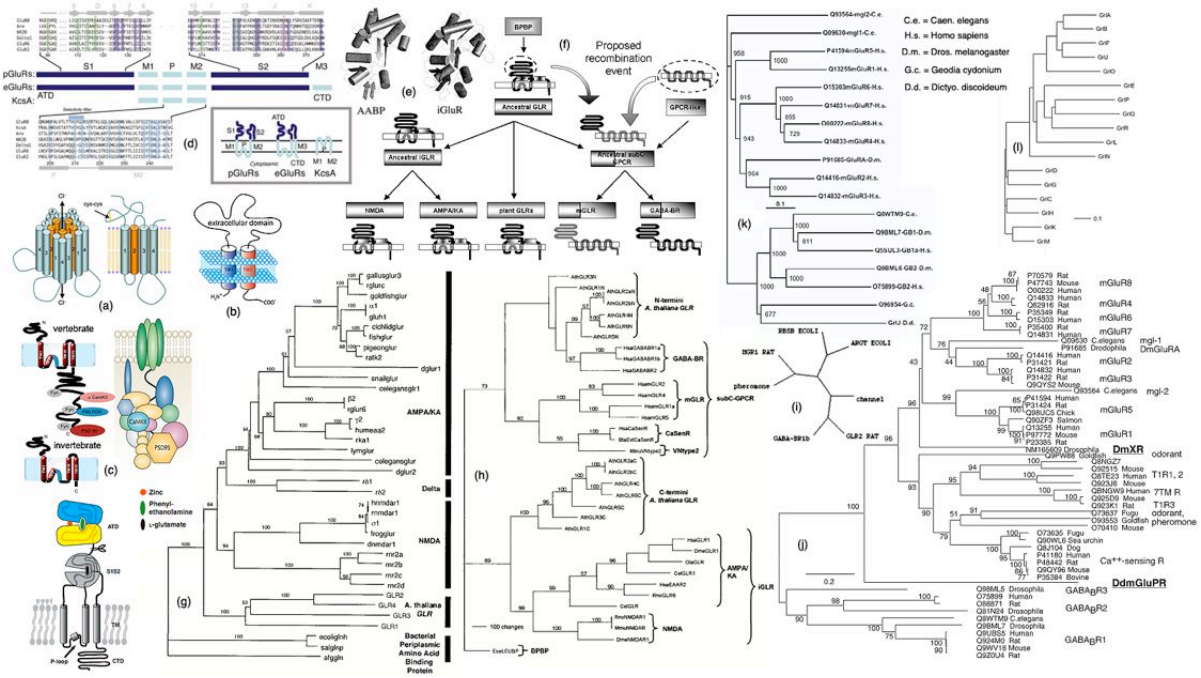


Fig: 27 The ligand gated ion channels consist of three evolutionary superclusters **(a)** The cysteine-loop receptors including 5HT3, GABAa and nicotinic acetyl-choline receptor, which are pentameric. The nicotinic acetyl-choline receptor occurs in vertebrates, insects nematodes and molluscs again suggesting an early common origin (Tsunoyama & Gojobori, van Nierop et al) **(b)** The ATP gated channels, which are active in trimers. P2X receptors are present in a diverse array of organisms including vertebrates, *Dictyostelium*, the platyhelminth *Schistosoma*, and the green alga *Ostreococcus* and possibly in *Drosophila* (North, Fountain et al, Burnstock & Verkhratsky, Dolezelova et al). **(c)** The ionotropic iGluR glutamate receptors NMDA, AMPA and kainate type, forming tetramers, in the case of NMDA consisting of two units each responding to glycine and glutamate (Ryan et al, Ryan & Grant, Karakas et al). NMDA recptors are shared by vertebrates, *Drosophila* and *Caenorhabditis* (Teng et al). **(d)** The membrane-spanning portions of iGluRs, including the GluR0 from cyanobacterium *Synechocystis*, and those of eucaryotes, consist of sections with sequence homology to the bacterial voltage-gated K^+ channel inverted so the extra-cellular orentiation is reversed (Chen et al). The “fly-trap” (Felder et al) binding domain to glutamate on the NMDA receptor has homology with the bacterial periplasmic amino-acid binding protein (Oh et al, Lampinen et al). **(e)** Homologous domains (Tikhonov D. & Magazanik). **(f)** This leads to a model of functional domain transfer to form the glutamate-binding region of both ionotropic and metabotropic glutamate receptors, including the plant ionotropic glutamate receptor form in *Arabidopsis*, confirming it entered eucaryotes before the divergence of plants, animals and fungi (Turano et al). **(g,h)** This evolutionary relationship linking prokaryotes and eucaryotes is confirmed in evolutionary trees with homolgies spanning both ionotropic and metabotropic glutamate receptors (Chiu et al, Turano et al). **(i)** Tree of bacterial periplasmic amino-acid binding proteins and related receptors in eucaryotes (Felder et al). **(j)** Evolutionary tree of metabotropic glutamate receptors showing that from the slime mold amoeba *Dictyostelium discoideum* as well as *Drosophila* and Vertebrate mGluRs (Taniura et al). **(k,l)** 17 member metabotropic GABAb family in *Dictyostelium discoideum* (Anjard & Loomis, Prabhu et al, Eichinger et al).

The many reports of increased social dominance in primates (Edwards and Kravitz, 1997) and improved mood and confidence in social interactions in humans after using drugs which increase serotonin levels are well documented (Kramer, 1993; Young and Leyton, 2002). In these higher animals, 5-HT continues in its role of a homeostatic regulator in adjusting the dynamic interactions of these many functions within the organism, and how the organism interacts with the outside world. Similarly, dopamine and nor-epinephrine pathways modulate reward and vigilance, forming a spectrum of fundamental strategic responses in humans now phenomenally elaborated into an extremely complex CNS, but nevertheless modulated in its major organismic feedbacks through the same signaling pathways already evident in the amoebae and other protozoa. While in mammals only neurons and mast cells secrete serotonin, all cell types possess serotonin receptors, emphasizing the fact that it plays a key role, not just in brain-generated emotion, but the entire bodily tone.

The serotonin systems are still in a state of rapid evolution. In the sea slug aplysia's nervous system there are only a few neurons that contain serotonin, and these neurons are large, with extensive connections. In the rodent brain, the 5-HT neurons are arranged in large groupings along the midline of the mescencephalon. The axons from these neurons ascend towards the forebrain in large bundles using mainly the ancient medial fore-brain bundle. In primates, the distribution of serotonergic neurons in the mescencepahlon is into smaller clusters of neurons. In addition, many of the axons from these neurons are now myelinated. This new arrangement facilitated more precise and rapid delivery of serotonin to forebrain targets (Azmitia, 1987).

Turning now to both metabotropic and ionotropic glutamate and GABA receptors, we find evidence of even more ancient origin in prokaryotes. Firstly the metabotropic glutamate and GABA receptors go back to the social amoeba Dictyostelium discoideum, where there is a family of no less than 17 GABA and a glutamate receptor involved in differentiation, showing these receptors too go back to single-celled eucaryotes.

The ionotropic receptors fall into three superfamilies: (1) the nictoninic and GABA receptors, as well as 5HT3, the cys-loop family, forming pentameric channels, (2) the ATP-binding channels, which also go back to amoebae, and (3) the tetrameric glutamate ionotropic receptors, including NMDA, AMPA and Kainate, which in the case of NDMA, have two types of monomer, binding glycine and glutamate respectively. The glutamate-binding “fly trap” section of both ionotropic and metabotropic glutamate receptors show homologies with the bacterial periplasmic amino-acid binding protein essential for maintaining bacterial molecular membrane sensitivity. The membrane-spanning section of the iGluRs also show homology with the bacterial voltage-gated K^+ channel, which appears to have been inverted in membrane orientation and inserted between the two extra-cellular glutamate-binding sections of the “fly trap”. These changes are already in place in the cyanobacterial GluR0 ionotropic glutamate receptor. Hence the two critical domains of this unit have arisen through genetic transfer of functional domains. The fact that an iGluR has also been found in *Arabidopsis* shows this class entered the eucaryotes before the plants, animals and fungi diverged. Elements of the protein signallinging pathways, such as protein kinase C, essential to neuronal synaptic contact likewise originated close to the eucaryote origin (Emes et al, Ryan & Grant). Likewise the *Dlg* family of postsynaptic scaffold proteins, which bind neurotransmitter receptors and enzymes into signaling complexes originated before the divergence of the vertebrates and arthropods but underwent two gene duplications in vertebrates leading to vertebrate cognitive complexity (Nithianantharajah et al).

13: Conclusion

In an era when humanity has decoded the human genome and come close to unravelling the cosmological theory of everything shaping the universe, the nature of subjective consciousness remains an enigma confounding the scientific description of reality, which remains the central abyss confronting our understanding of nature. We need to open the doors of perception to understand the conscious condition.

In an era in which humanity has developed weapons of mass destruction, and is impacting on the planetary biosphere, potentially causing irreversible climatic change and a mass extinction of biological and genetic diversity, we need above all to come to better terms of understanding of our place in the universe, the role of sentient life in it and how to protect our unborn future generations.

For both these reasons, we cannot afford to taboo research and discovery into the nature of entheogens, which may form a central part of the solution to both these pressing problems. The capacity to experience the entheogenic state should be accepted as a fundamental right of every sentient being. Society needs to find safe, supportive and conducive ways of bringing the enthoegens back to the revered place they have held in virtually all societies throughout history.

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